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COMMENTARY

Has in-vitro fertilization made salpingostomy obsolete?

There are some tubal causes of infertility where surgery has virtually no chance of success. These include patients who have had bilateral salpingectomies, those who have bilateral, multi-site tubal obstruction and those with obstructed tubes amid dense pelvic fibrosis (frozen pelvis). At the other end of the scale, reversal of mechanical sterilization will succeed in 50–80% (Jansen, 1987). Thus, the choice between in-vitro fertlization (IVF) and tubal surgery is easily made at the extremes of the surgical prognostic range, but this decision is contentious for women with an intermediate prognosis. The surgical outlook for pathologically blocked tubes depends mainly on the extent and nature of tubal damage, but surgical technique and other factors affecting fertility, such as age, also influence results. Proximal blockage of otherwise healthy tubes is a very rare condition (Grant, 1971) with a good surgical prognosis (Donnez, 1986; Levinson, 1981) and IVF should be second-line treatment for such patients. The same applies to patients where each tube is blocked only at its fimbrial end, provided that good prognostic features are present including minimal tubal dilatation and minimal pelvic adhesions (Grant, 1971; Hulka, 1982). Unfortunately, these patients with a good outlook make up only 10% of all those presenting to tubal surgeons (Watson *et al.* p. 561, this issue). Typically, the prognosis for surgery is much worse and it is reasonable to ask whether most patients with more severe tubal damage should undergo an operation in the first instance or whether they should be offered IVF as primary treatment. The role of IVF is controversial (Lilford & Dalton, 1987) but the choice of primary treatment must be influenced first by the probability of success (which is best defined as birth of a baby who survives the neonatal period) after surgery or acceptance in an IVF programme; second by the side-effects (mortality or morbidity) of each method of treatment and third by the financial costs of each method.

Effectiveness of treatment

A report in this issue (p. 561) gives a pregnancy rate of 10% (and a 5% chance of a viable pregnancy) for the surgical treatment of bilateral distal tubal obstruction. Follow-up rates in this study were high (90%), thereby minimizing bias due to selective follow-up of successful cases. The literature review quoted in this study includes viable pregnancy ('success') rates which range from these low levels up to 40%, but only three of the 19 articles that quote third-trimester pregnancy rates record success rates of over 30% and these are all small series. These results include the relatively small proportion of patients with good prognostic factors. The success rates for most patients who have a worse outlook for surgery, and among whom the controversy about the best primary treatment applies, would be worse.

There are many potential biases in the reporting of IVF success rates. *Reporting* bias is best reduced by quoting 'take home baby' rates but in reality many reports use total pregnancies as the numerator and this may overestimate the effectiveness of IVF, especially if 'chemical' pregnancies are included, since 26% of these will miscarry (Page, 1989a). IVF 'success' rates are usually quoted per attempted cycle or per embryo transfer (33% of cycles do not reach this stage) (Fishel *et al.* 1986). However, the most appropriate denominator for comparative purposes is the number of couples accepted onto an IVF programme. *Selection* bias arises from the greater mean age and lower intrinsic fecundity of couples referred for IVF after failure of tubal surgery—the treatment which is given first will tend to differentially select out the most fertile couples. Poor funding of IVF centres results in many cost-cutting steps which may also under-estimate the potential effectiveness of this treatment. Furthermore, results of tubal surgery must be compared with those where tubal blockage was the indication for IVF, since the overall success rates of this form of treatment will usually be biased unfavourably by inclusion of patients with oligospermia or endometriosis.

The ultrasound confirmed pregnancy rate for IVF is given at 10% per attempted egg retrieval by the Interim Licensing Authority (1989) in the U.K., while exactly the same figure is quoted in the Netherlands on the basis of treatment cycles started (Haan, 1989). Furthermore, IVF pregnancy rates of 25-30% per cycle where egg collection is attempted are achievable in experienced units in the U.K., North America and Australia (quoted by Jansen, 1987) and the graph relating pregnancy rates to the number of cycles of treatment is almost linear until about four cycles have been attempted (Dubois *et al.* 1987), although we must bear in mind the possibility of publication bias when quoting results from individual units rather than National Registers. Nevertheless, in a study comparing IVF and tubal microsurgery, cumulative pregnancy rates were much higher (54%) with the former (Dubois *et.* 1987). Even allowing for miscarriage and neonatal death, a single cycle of IVF would seem to be more successful than surgery for the treatment of distal tubal blockage in all but that small proportion of women who have good prognostic features for surgery.

Side effects

Both methods of treatment are safe but surgery involves more nights in hospital and a longer period of convalescence. IVF is stressful but the disappointment of failed tubal surgery should not be under-estimated simply because clinic staff are protected from day to day contact with the unhappy patients. Furthermore, formal psychometric investigation does not show pronounced adverse effects from IVF treatment but rather a slight 'uniting effect' on the couple (Haan, 1989). However, we should be aware of a possible *'Hawthorne effect'* in such studies (observations of an outcome may affect the outcome) and no formal comparisons of the long-term psychological effects of these treatments have been made. Both procedures may lead to tubal pregnancy. IVF has the particular feature of producing frequent multiple pregnancies although the use of cryostorage has been associated with a tendency towards replacement of fewer embryos and many infertile couples might see twins as a blessing rather than a complication.

Monetary costs

Given that IVF is likely to be more effective than tubal surgery for all but a small number of identifiable patients, and given that neither treatment has demonstrably worse side-effects, it could be argued that IVF is the best treatment. Although rich couples are in a position to make an informed choice between these alternatives, poorer women can only do so if both methods are externally funded. Clearly, budget holders of purchasing authorities and others who act as proxies for consumer preference will wish to take into account not only the side effects and effectiveness of each treatment, but also their relative costs. Cost to patients, such as loss of earnings while attending for treatment, are also important.

Tubal surgery has similar costs to other major elective operations and we found that patients in Yorkshire spend an average of 10 days in hospital using 1·5 h of theatre time while a number of patients (46% in Yorkshire) undergo post-operative investigations (salpingogram or laparoscopy). The approximate financial implications of these figures are given in Table 1, at current prices, each operation is calculated to cost slightly in excess of £1000. (This figure is an under-estimate as our cost of in-patient care is averaged over the whole hospital which contains many long-stay beds and we do not include capital charges, porters and administration) Given a successful pregnancy rate for salpingostomy of 5%, the cost for each baby born as a result of surgery in our region is at least £20 000, and this figure would be higher still if we were to confine our attention to the patients for whom treatment is controversial, ie , those with poor prognostic features for surgery.

IVF is expensive because of staff time and drugs and because the cumulative interest on start-up capital must be properly discounted. *Prices* for IVF can exceed £2000 per cycle, but *costs* are lower than this. Page (1989b) has studied three British Units and calculated a cost of £366 per cycle, £11 000 per viable pregnancy and £8800 per baby. The latter figure is lower than

Table 1. Costing of tubal surgery at St. James's Hospital, Yorkshire

Component of treatment	Source of financial information	Cost	Comment	Calculation
Hospital bed per night (average stay)	Hospital finance dept.	£85/day	Average over whole hospital	£85 × 10·1† = £858·50
Tubal surgery	RCCS for cost and theatre registrar for time.	£90/h	Average theatre time 1·6 h (electricity not included)	£90 × 1·6 = £144·00
Postoperative hysterosalpingogram*	X-ray dept.	£30	24% had this investigation*	£30 × 24/100 = £7·20
Laparoscopy*	RCCS and theatre registrar	£90/h	Average theatre time 0·5 h, 22% had this investigation	£90 × 0·5 × 22/100 = £9·90
				TOTAL = £1019·60

*These were frequently done to clarify prognosis for patients with a view to referral to IVF service earlier than might have been warranted if the tubes were patent.

†The figure of 10·1 nights included any further admissions after tubal surgery such as interval removal of stents or tubal patency testing by laparoscopy and dye.

RCCS, revenue consequences of capital schemes from Yorkshire Regional Health Authority (YRHA) Administration Department.

the price per pregnancy because of the occurrence of multiple births, but there are knock-on costs of neonatal care which add 20% to the cost of each successful pregnancy (Haan, 1989). The non-profit making Oxford Assisted Reproduction Clinic (Bromwich *et al.* 1988) charges £1050 per cycle (including drugs) in which oocyte recovery is attempted and it is claimed that this is a true cost with no hidden subsidies (P. Bromwich—personal communication). In the same year Australian costs were $4000 per IVF 'cycle' and $20 000 for each child born as a result of this technology (Trounson & Wood, 1987). The Kings College Hospital Unit charges £1200 per *embryo transfer* compared with £2000 for tubal surgery. These figures suggest that tubal surgery is somewhat more expensive than a single completed cycle of IVF and the results of an economic appraisal in France suggest that IVF was competitive at F 5526 per cycle where stimulation was attempted compared with F 16 720 for tubal microsurgery (Monrozies *et al.* 1987). A study in the Netherlands found similar cost-effectiveness for IVF and tubal surgery (Haan, 1989). From a health service procurer's point of view IVF seems a better buy for the treatment of distal tubal obstruction once the small proportion of women with a good surgical prognosis have been excluded; it is difficult to say whether IVF or surgery has the worse side-effects, while IVF appears to have a better success rate at a lower cost per successful outcome. Furthermore, the cost-effectiveness of IVF will improve with better funding, experience, medical advances (eg., use of growth hormone) and cryopreservation of embryos not replaced in the first cycle of treatment. We think that clinicians will increasingly reserve salpingostomy for: the small number of women with bilateral distal obstruction with minimal tubal dilatation or adhesions and those for whom IVF is not available.

We think that purchasing health authorities/health insurers should make IVF more widely available (Dalton & Lilford, 1989; Page & Brazier 1989). They should purchase this service rather than tubal microsurgery for most patients with tubal blockage.

Where surgery is indicated, we suspect that laparoscopic procedures, such as those using CO_2 laser (Donnez & Nisolle, 1989), will replace open laparotomy on the grounds of effectiveness (which appears to be at least as good), morbidity and cost. Whatever method of treatment is chosen, it is essential that patients are referred to an infertility centre without delay, since we see too many patients whose prospects for pregnancy have been damaged by procrastination.

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The results of tubal surgery in the treatment of infertility in two non-specialist hospitals

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Summary. The results of surgery for tubal damage, other than reversal of sterilization, were studied in two large hospitals. This is the first recent study from centres claiming no special expertise in this surgery. An unusually high follow-up rate was obtained. The term pregnancy rate for patients operated on for bilateral distal tubal occlusion was 4%. The success rate is lower than the lowest reported, overall success rates for *each cycle* of in vitro fertilization (IVF) and very much lower than cumulative term pregnancy rates for tubal surgery reported by most other authors. Patients with distal tubal occlusion but minimal adhesions had the best prognosis. Our results suggest that, provided *in vitro* fertilization is available, only those patients with good prognostic factors should undergo tubal surgery. These represent the minority of all patients with non-iatrogenic tubal blockage.

The results of tubal surgery reported in the last two decades have come from specialist centres. However, most infertility surgery is done in general hospitals. Worse results might be expected from such centres, not only because of lower technical expertise and less rigorous case selection but also because the opportunities for more complete (and therefore less biased) follow-up are greater in non-specialist centres catering for local needs. This study was undertaken to determine success rates for tubal surgery in two large hospitals with no special sub-specialist expertise; one teaching and one district general.

It is known that pregnancy rates for reversal of sterilization can be good (50–80%) (Winston 1977). We have not addressed this issue at all and have limited our attention to pathologically damaged tubes. While reported success rates for tubal surgery as a whole are encouraging, many of these patients have adhesions or unilateral tubal damage rather than bilateral obstruction. In the absence of control data it is impossible to say how many pregnancies following division of adhesions or unilateral tubal surgery can be attributed to treatment. Therefore, we paid particular attention to the success rates of tubal surgery in patients where both tubes were blocked. Patients who had bilateral tubal occlusion were further classified according to the site of blockage and severity of tubal damage.

Subjects and methods

The names of all patients undergoing surgery for

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infertility at Bradford Royal Infirmary (BRI) between 1980 and 1986 inclusive, and St James's University Hospital, Leeds (St James's) between 1981 and 1985, were obtained from the theatre registers. Reversal of sterilization was excluded. We found that pre-operative tests of tubal patency (laparoscopy and dye and/or hysterosalpingogram (HSG)), progesterone assays and seminal analysis (usually backed up with a post-coital test) had been done on all patients.

Letters containing pre-stamped envelopes were sent to the general practitioners of all 20 patients who could not be traced through the general gynaecology, antenatal or regional in vitro fertilization clinics. Reminders were sent if no reply was received.

Follow-up was regarded as being adequate if one of the following criteria was satisfied: (i) there had been a successful pregnancy; (ii) bilateral tubal occlusion had been confirmed after the operation by an HSG or a laparoscopy; (iii) there had been an attempt at IVF; (iv) the menopause had been confirmed biochemically; (v) a hysterectomy had been performed; (vi) a *minimum* of 12 months confirmed follow-up without pregnancy.

In reality follow-up was usually much longer with a mean of 40 months. We also recorded the duration of hospital stay, theatre time (from surgical register) and follow-up examinations.

When the patient had had both a miscarriage and a term pregnancy, only the more successful outcome was included in the results.

We excluded one patient who was operated on for bilateral adhesions because her previously normal husband had developed azoospermia following unilateral orchidectomy for testicular teratoma in the first month after tubal surgery.

Results

After excluding one patient, 50 had had infertility surgery at St. James's and 32 at the BRI. Of these 82 patients, 33 had primary infertility. The mean duration of infertility before surgery was 5 years (2–11). The mean age was 27 years (19–38).

The presence or absence of tubal occlusion, along with the site of any such occlusion, was determined from the case records. There were four major groups of patients depending on whether one, both, or no tubes were patent and on the site of any obstruction (Table 1).

Follow-up (as defined above) was achieved for all but five of the patients (94%). Average follow-up (of patients who did not fall into groups 1–5 above) was 3 years and 4 months. The remaining five patients had moved out of the area and could not be traced.

Twelve patients conceived and nine were delivered in the third trimester of pregnancy. This represents 15% and 11% respectively of the 82 patients studied and 16% and 12% of those with adequate follow-up. One patient has had two babies. Adhesiolysis was performed in 19 patients (18 with adequate follow-up) and four conceived and all four gave birth—a success rate of 21%.

If only patients where both tubes were blocked are included, then 8 of 63 conceived and five carried a pregnancy into the third trimester (13% and 8% of all patients and 14% and 8% of the 59 patients with adequate follow-up).

If those with patent distal tubes, but bilateral proximal blockage (an over-diagnosed condition known to have a good prognosis) (Donnez 1986 & Levinson, 1981) are also excluded then 5 of 57 patients conceived and only two had a third trimester delivery (9% and 3% respectively of all patients). These proportions are 9% and 4% if only the 53 patients with adequate follow-up are included. Four of the 40 patients with bilateral occlusion but with no proximal occlusion conceived (10%). Two of these had a third trimester delivery (5%). If only the 37 patients with adequate follow-up are included then the pregnancy and delivery rates are 11% and 5% respectively.

When the 40 patients with bilateral distal occlusion, but with no proximal occlusion, were further subdivided according to the presence or absence of bilateral hydrosalpinges and the recorded degree of adhesions, it was found that both term pregnancies occurred among 12 patients recorded as having minimal adhesions. These patients both had a mild degree of hydrosalpinx. Only five patients had both minimal adhesions and at least one undilated fallopian tube.

The average duration of hospital stay was ten nights including any post-operative procedures such as interval laparoscopy and dye tests. The average theatre time was 1·6 h. Overall 24% had

Table 1. Categories of patients with tubal factor infertility who underwent surgery

Category	Pathology site	Usual surgery
A	At least one tube patent	Adhesiolysis
B	Bilateral distal blockage (or blockage of the remaining tube)	Fimbrioplasty/salpingostomy
C	Bilateral proximal blockage (or blockage in a remaining tube)	Tubo tubal reanastomosis Cornual re-implantation
D	One side proximal damage the other side distal or blockage at two sites in one tube with blockage of contralateral tube	Mixture of procedures

a post-operative hysterosalpingogram and 22% underwent post-operative laparoscopy.

Discussion

One in six couples need specialist help at some stage because of infertility and 14% of these are judged infertile because of tubal factors (Hull *et al.* 1985). Tubal surgery was first performed in 1884 by Schroder (Siegler, 1977) with the first attributed term pregnancy occurring a quarter of a century later. Tubal surgery in the hospitals in this study was performed by general gynaecologists (consultants or senior registrars) without the aid of an operating microscope, although magnifying glasses were used by most surgeons. Our study gives a more realistic estimate of the expectation of successful pregnancy for most of the nation's patients than the published figures from specialized units. There are three main reasons which together or separately might explain why these results are worse than in previous series, all of which come from units with a specialist interest in this type of surgery.

The first is that specialized units are likely to be more selective (realistic?) in the categories of patients accepted for surgery and Grant (1971) noted that pregnancy rates were considerably higher for highly selected cases.

A second possible reason for the relatively low proportion of recorded successes in this series is the high follow-up rate which we achieved. A low follow-up rate might bias results, reported in terms of cases followed, in a favourable direction because: (1) families with children may be more likely to remain within the area; (2) where the family has moved, good news is more likely to be transmitted by the patient or the attending obstetrician when pregnancy occurs.

Many of the published studies do not quote a follow-up rate (Wallach *et al.* 1983; Siegler & Kontopoulos 1979; Russell *et al.* 1986) while many others (Gomel, 1978 and Jansen, 1980) have very poor follow-up rates. Schoysman (1984) is forthright, he states '. . . large percentage of cases of which we have no information at all, the lack of this information most likely influences final outcome of tubal surgery' He achieved only a 75% follow-up in his study. Two factors enabled us to achieve a high follow-up rate. Firstly, a large number of patients who failed to attend the follow-up clinic could be traced through the in vitro fertilization clinic, based at St. James's, to which they had been subsequently referred. The second factor is that we made strenuous efforts to trace the remaining patients through their general practitioners. People prone to tubal damage tend to be highly mobile, so despite our efforts five still have an unknown outcome. The mean duration of follow-up (40 months) compares favourably with other reported series. Other recent studies include quoted follow-up periods of 6 months (Hulka, 1982), 9 months (Verhoeven *et al.* 1983) and 1 year (Wallach, 1983).

The third possible reason (and the reason most frequently invoked by sub-specialists) for the greater reported success from surgeons with a special interest in tubal surgery is their greater training and expertise. Although this is likely to contribute to reported success rates, we are not convinced that this is the most important factor. One of the surgeons who operated on many of the patients in this study has recently looked into the results of patients on whom he performed reversal of sterilization. He found term pregnancy rates of >90% among 22 patients (Macdonald, personal communication) undergoing reversal of clip or ring sterilization and these excellent results argue against the conclusion that poor technique was the main reason for our relatively poor results. Specialist centres fre-

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Table 2. Previous studies of surgery for bilateral tubal distal obstruction

First author and year of publication	Longitudinal or retrospective	Gross or Micro	Number			Ectopic (%)	Pregnancy (%)	Intrauterine pregnancy (%)	Term pregnancy (%)	Comments
			Operated on	In study	% Follow-up					
Mage (1986)	L	MS	–	70	–	9	–	26	–	Patients with 'combined surgery' not in study Not all had total occlusion.
Daniell (1986)	L	MS and laser	–	48	–	2	–	–	19	
Russell (1986)	R	MS	–	68	–	17	–	42	–	This is a long-term follow-up of DeCherney's study (1981)
Donnez (1986)	L	MS	–	83	–	7	–	31	–	No surgery on 'thick-walled hydrosalpinx'
Tulandi (1984)	L	MS and laser	–	45	–	2	–	22	–	
	R	G	–	45	–	11	–	17	–	
Schoysman (1984)	R	MS	63	49	78	–	41	–	–	'Severe pathology'—not operated on.
	R	G	131	99	76	–	26	–	–	
Rock (1984)	L	MS	–	206	–	3	–	–	9	
Wallach (1983)	R	–	–	24	–	8	–	–	21	143 patients in total; 24 with bilat. distal obstruction
Mage (1983)	R	MS and laser	68*	68	–	4	–	–	21	
Bellina (1983)	R	MS	–	33	–	–	35	–	–	
Verhoeven (1983)	R	MS	–	143	–	2	–	–	20	
Frantzen (1982)	R	MS	85*	85	–	–	–	–	14	

Hulka (1982)	L	MS	61*	61	90	–	–	–	10	
Fayez (1982)	R	MS	–	20	–	–	40	–	–	
	R	G	–	42	–	–	25	–	–	
Larsson (1982)	L	–	–	45	–	0	–	–	36	
DeCherney (1981)	L	MS	–	18	–	0	–	–	33·3	
Spadoni (1980)	L	G	–	18	–	0	–	–	44	'Duration of infertility at least 3 months' Distal tubal disease—not all occluded
Jansen (1980a)	R	G	–	112	–	–	15	–	–	
Jansen (1980b)	R	G	105	86	82	1	–	–	13	
Betz (1980)	R	G	–	20	–	–	–	5	–	
Siegler (1979)	R	G	–	15	–	20	–	–	13	
	R	MS	–	23	–	13	–	–	22	
Rock (1978)	R	G	–	99	–	6	–	–	16	99 out of 158 referrals met criteria for surgery.
Gomel (1978)	R	MS	50	41	82	–	–	–	22	% figures in study from follow-up not total number operated on.
Hulka (1978)	R	G	–	56	–	–	11	–	–	Complete bilateral obstruction 27 patients not included in study
Comninos (1977)	R	G	–	30	–	–	28	–	–	
David (1976)	R	G	–	23	–	–	–	–	4	
Grant (1971)	R	G	217*	217	–	2	–	–	11	
Jessen (1971)	R	G	–	23	–	–	–	–	26	
Ozaras (1968)	R	G	–	106	–	2	–	–	1	

*Paper states that patients lost to follow-up assumed not pregnant. MS = Microsurgery G = Macroscopic (gross).

quently carry out microsurgical techniques which allow for the use of very fine suture materials and this may lead to improved results (Tulandi *et al.* 1984; Siegler & Kontopoulos, 1979) , but delicate surgery performed without magnification can produce equivalent results (Fayez & Suliman, 1982). Furthermore, laparoscopic salpingostomy produces equally good results, again suggesting that use of the microscope *per se,* adds little to the success of salpingostomy (Donnez & Misolle, 1989).

The term pregnancy rate for adhesiolysis in patients with patent tubes was 21% (80% confidence interval 17%–25%). In other series this is the most successful operation (Bellina, 1983; Schoysman, 1984; Fayez & Suliman, 1982). However, it is impossible to say how many of these patients would have conceived without surgery, or whether infertility was enhanced or reduced by this intervention. In this study one such patient was found to have bilateral distal tubal occlusion when a hysterosalpingogram was obtained 6 months after salpingolysis. Laparoscopic tubal surgery is said to have an advantage for such patients (Gomel, 1975).

The results for isolated proximal tubal damage are good; 50% (24%–76%) success but false positive diagnosis is common. Grant (1971) found that when 50 cross sections of each excised tubal portion were examined microscopically by an experienced pathologist, occlusion was confirmed in only half of the patients. This process took half a day per excised tubal specimen and has never been repeated.

Repair of bilateral distal tubal obstruction was the most unsuccessful operation with 3·5% term pregnancies overall and 5% if those with both proximal and distal obstruction are excluded.

Most series give term pregnancy rates for surgical correction of bilateral distal occlusion of approximately 20% (Table 2). Three papers have shown results as disappointing as our 5%. David *et al.* (1976) found that only one of 23 patients (4%) had a term pregnancy after surgery for bilateral distal tubal occlusion. Of 20 patients operated upon by Betz (1980) for non-iatrogenically damaged distal occlusion, only one achieved an intrauterine pregnancy. Ozaras (1968), in a series of 106 patients, reported only one successful term pregnancy.

There was one ectopic pregnancy in our series of 57 bilateral salpingostomies. Ectopic pregnancy rates after bilateral salpingostomy have been quoted as being as high as 30% in one series (Rock *et al.* 1984) and are usually >5% (Russell *et al.* 1986). Jansen (1980a) stated 'the occurrence of abortion or ectopic pregnancy should not be interpreted as an indication that a viable pregnancy is likely to follow. More often than not it is the only pregnancy'.

Rock (1978) found that pregnancy rates were related to the degree of tubal damage and extent of pelvic adhesions. Mage *et al.* (1986) confirmed this conclusion and recommended that patients with extensive epithelial damage could be excluded from surgery by the use of pre-operative salpingostomy and referred directly for IVF. However, this option is realistic only for those for whom IVF is available and patients who are unable to obtain this service will often ask for tubal surgery even if the quoted chances of success are as low as 1%. In this series, 16% of patients with distal blockage but minimal adhesions had term pregnancies and none of the patients with more extensive adhesions and blocked tubes had satisfactory outcomes. Only 30% of patients with bilateral distal occlusion were recorded to have minimal adhesions. An even smaller proportion of patients can be expected to fulfil the following good prognostic criteria: (1) minimal adhesions; (2) blockage at only one end of the tube, (3) no hydrosalpinx or unilateral hydrosalpinx; (4) normal tubal epithelium confirmed at salpingostomy.

Only five of the 57 patients with bilateral blockage in this series satisfied criteria 1–3 inclusive and the number fulfilling all four criteria would be lower still.

There has been controversy recently about the relative roles of tubal surgery and IVF in the treatment of tubal factor infertility (Lilford & Dalton 1987; Winston & Margara, 1987; Lilford & Dalton 1987; Bromwich *et al.* 1988). This study should shift weight towards the arguments for IVF except for the very small number of women with minimal tubal damage. We anticipate that laparoscopic surgery will replace laparotomy in these women. In contrast to tubal surgery where success rates have been static for the last 20 years (Table 2), it is likely that pregnancy rates will continue to improve with IVF.

We consider that IVF, which has a success rate of 20–35% per cycle in women with tubal disease (Lilford & Dalton 1987; Bromwich *et al.* 1988), should be available more readily through the NHS. Even the national success rate of 10·1% *per cycle,* (Voluntary Licensing Authority for Human In Vitro Fertilization and Embryology,

1989) which includes poor risk cases (oligospermia/endometriosis) and results from many fledging underfunded centres, exceeds the overall sucess rates reported for non-iatrogenically blocked tubes in this study. Tubal surgery should not be used as first line treatment except for the small minority with good prognostic features (see above). We have shown that the number of such cases is very small and two or three units within the country could cope with the demand. At present properly funded NHS IVF is present in two regions only and but tubal surgery is carried out in all regions and in many district hospitals. We think that this situation should be reversed.

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Luteal phase deficiency: ultrasonic and biochemical insights into pathogenesis

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Summary. Serial ovarian ultrasound and daily assessments of plasma concentrations of pituitary and ovarian hormones were used to investigate ovarian function in 175 women with unexplained infertility. Their endocrine and ultrasound profiles were compared with similarly derived data from 43 normal volunteers. Fifty-one (29·1%) of the study group showed subnormal luteal phase rises in progesterone concentrations, described as poor progesterone surge (PPS) cycles. Within this group, 23 women (45·1%) demonstrated luteal cyst formation, a pattern not seen in any of the control cycles. High concentrations of follicle stimulating hormone (FSH) and reduced concentrations of oestradiol (E2) were observed in the follicular phases of the PPS cycles suggesting that the phenomenon is a product of abnormal follicular metabolism. An association of PPS with infertility exists, perhaps related to a combination of disturbances in the follicular micro-environment compromising oocyte quality, a failure of oocyte release, and impaired endometrial receptivity.

Luteal phase deficiency and its role in infertility has generated much debate centred on problems of definition and diagnosis (Fleming *et al.* 1981). Histological assessment of the endometrium, single and multiple biochemical assays of progesterone and basal body temperature changes all have limitations. Serial ovarian ultrasound and daily measurements of plasma concentrations of pituitary and ovarian hormones permit detailed assessment of ovarian function and provide an opportunity to investigate the pathophysiology of cycles demonstrating luteal phase deficiency.

Preliminary studies (Fleming *et al.* 1981) have suggested that luteal dysfunction is not unusual in women with unexplained infertility. The aim of this study was to determine plasma gonadotrophin and ovarian steroid hormone profiles, and ovarian follicular growth patterns assessed by serial ultrasound, in a large population of women with unexplained infertility, and to compare them with data generated from a normal control population.

Subjects and methods

The study included 175 women with unexplained infertility (>3 years duration; normal menstrual

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rhythm with cycle length 24–41 days; normal laparoscopy within the previous 2 years; normal partner; normal post coital test, no sexual problems). The women were investigated with a fixed protocol.

Blood samples

A blood sample (10 ml) was taken at the same time daily from each woman, throughout the menstrual cycle and each sample was separated and the plasma stored at −20°C for retrospective analyses. Sensitive, specific and precise radioimmunoassays for 17β-oestradiol (E2), progesterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) were carried out on all samples (Coutts *et al.* 1981). All samples from a cycle were analysed within a single batch to eliminate inter-assay variation

Ultrasound scans

Scans were performed by a single operator (MPRH) using a B-mode static scanner (Nuclear Enterprises 4201, Fischer, Edinburgh) with a 3·5 MHz abdominal probe, calibrated to 1540 m/s. The full bladder technique (Hackeloer *et al.* 1979) permitted inspection of the follicle which was measured in three dimensions, follicular diameter being expressed as a mean of these three measurements. Scans were carried out from the eighth day of the cycle and after identification, any developing follicle was monitored daily through the periovulatory period to determine if the characteristic infilling of the corpus luteum occurred (Hackeloer *et al.* 1979). Thereafter women were scanned every 48 h until the end of the cycle. Not all women could attend as frequently as this ideal schedule demanded but, in practice, each woman had no fewer than four scans in the peri-ovulatory period and three in the luteal phase.

Control group

Forty-three volunteer women were investigated using the same schedules, as described above for those with unexplained infertility. Criteria for inclusion were: normal menstrual rhythm (24–41 days) over the preceding 6 months; no history of gynaecological disease; no oral contraceptive use over the previous 6 months and no sexual activity during the cycle of investigation. Their ages ranged from 18–36 years (median 26 years). To our knowledge at least 21 of the 43 volunteer women have since conceived.

Analyses and statistics

Cycles were compared after orientation around the day of the LH peak (day 0); days before this (follicular phase) were denoted negative, and after this (luteal phase) positive. A progesterone index was calculated for the early luteal phase of each cycle. This index was the sum of the plasma progesterone concentrations from days +2 to +6 in the study cycle, expressed as a percentage of the mean concentration in the control population over the same period. No assumption was made regarding the distribution of the data and, except where indicated, a non-parametric analysis (Wilcoxon rank sum test) was employed.

Some of the study cycles showed subnormal luteal phase rises in plasma progesterone and cycles with progesterone concentrations >1 SD below the normal mean on more than 2 days, between days +1 and +5 were described as demonstrating a poor progesterone surge (PPS).

Results

Of the 175 women with infertility 51 (29%) were found to have PPS profiles.

The age of these women was similar to the rest of the group with unexplained infertility and ranged from 22–40 years (median 30 years). Follicular phase length (first day of menses up to and including day 0) ranged from 8–27 days (median 15 days) while median luteal phase length (day +1 to day before onset of next period inclusive) was 15 days (range 11–18 days). These cycle characteristics were similar to those found in the control group.

Figure 1 illustrates the early luteal phase (days +2 to +6) plasma progesterone concentrations in the infertile group as a whole, compared with the control cycles. Although the sum of progesterone concentrations over this period was slightly reduced in the infertile group, this difference was not statistically significant. In the later part of the luteal phase, progesterone concentrations in the infertile and the volunteer women were similar.

The hormonal and ultrasound data relating to the PPS cycles are shown in Figs. 2 to 6, with the median values for the PPS cycles plotted against the 95% confidence limits of the control data, represented by the shaded area on each graph.

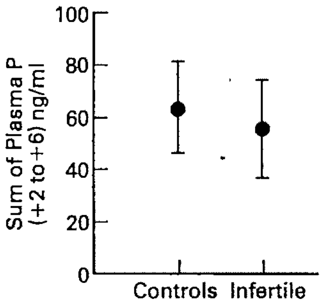

Fig. 1. Sum of plasma progesterone (P) concentrations (ng/ml) (days +2 to +6) in the infertile women (n = 175) compared with the volunteer control women (n = 43). (Bars represent means ± 1 SD.) No significant differences between the groups (unpaired student's t-test).

Statistically significant differences between the study cycles and the control data are indicated.

Progesterone

In justification of the PPS definition, progesterone concentrations (Fig. 2) were reduced for the greater part of the early to mid-luteal phase. The impairment of progesterone output by the corpus luteum was further confirmed by a significant reduction in the progesterone index (median 61·0, control 100·0, $P<0{\cdot}001$). In the later luteal phase, after day +9, mean progesterone concentrations were not reduced and if anything were slightly higher than the normal range.

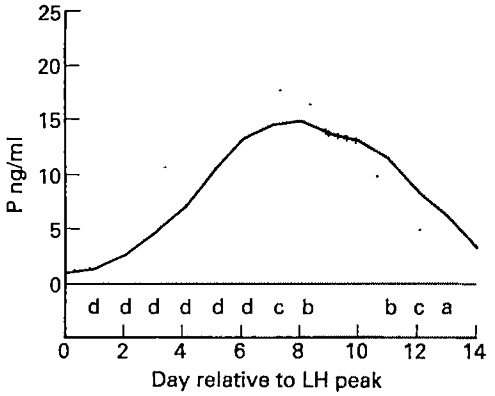

Fig. 2. Median plasma progesterone (P) concentrations (ng/ml) (days 0 to +14) in poor progesterone surge (PPS) cycles (n = 51) Shaded area represents 95% confidence limits of the control population (n = 43). (SI conversion: ng/ml×3·180 = nmol/l) Significance (Wilcoxon rank sum test): a = $P<0{\cdot}05$, b = $P<0{\cdot}02$, c = $P<0{\cdot}01$, d = $P<0{\cdot}001$.

Oestradiol

In the early follicular phase, plasma E2 concentrations in the PPS cycles were in the low normal range. In the late follicular phase (days −5 to −1) they were significantly reduced (Fig. 3) with the median peak E2 level (day −1) 205 pg/ml (753 pmol/l), (control 220 pg/ml (808 pmol/l), $P<0{\cdot}05$)). The E2 concentration on day 0 was within the normal range. The profile in the luteal phase was similar to that of the control cycles.

FSH

FSH concentrations were high throughout the follicular phase, significantly so on days −10, −6 and −3 (Fig. 4). Median peak concentration (day 0) did not differ from normal. In the luteal phase, high concentrations were again observed, significant from days +4 to +10.

LH

Median plasma LH concentrations were high throughout the cycle (Fig. 5), significantly so on days +5 and +7. Peak LH concentrations did not differ from normal.

Follicular diameter

The profiles of follicular diameter in the PPS group, before the LH peak, showed a linear growth pattern, in the low normal range (Fig. 6). This was similar to the E2 profile already described. Although the observed difference in

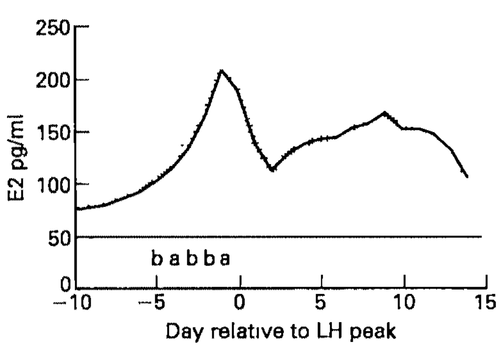

Fig. 3. Median plasma 17β-oestradiol (E2) concentrations (pg/ml) (days −10 to +14) in poor progesterone surge (PPS) cycles (n = 51). Shaded area represents 95% confidence limits of the control population (n = 43). (SI conversion pg/ml×3·671 = pmol/l) Significance (Wilcoxon rank sum test): a = $P<0{\cdot}05$, b = $P<0{\cdot}01$.

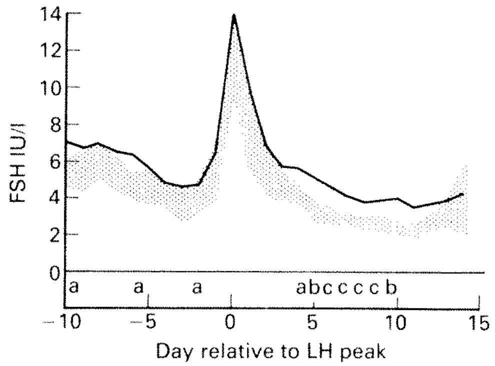

Fig. 4. Median plasma follicle stimulating hormone (FSH) concentrations (IU/l) (days −10 to +14) in poor progesterone surge (PPS) cycles ($n = 51$). Shaded area represents the 95% confidence limits of the control population ($n = 43$). Significance (Wilcoxon rank sum test): a = $P<0{\cdot}05$, b = $P<0{\cdot}02$, c = $P<0{\cdot}01$.

diameter on day −1 was statistically significant (median 18·0 mm, control median 20 mm, $P<0{\cdot}01$), the maximum diameter seen on day 0 (19·0 mm) was similar to that in the control population.

Following the LH peak, 23 (45%) of the PPS cycles demonstrated luteal cyst formation; the normal infilling and disappearance of the follicle as it became a corpus luteum was not seen, the follicle retaining its cystic appearance at least until day +5 and in many cases throughout the luteal phase. The diameter of the luteal cyst was calculated on the basis of the mean of all diameters measured between days +5 and +8. In five of the luteal cyst cycles (22%) some evidence of follicular shrinkage was seen at the time of the LH peak but most of them (78%) elaborated a pattern of cyst formation where no periovulatory follicular reduction in size occurred. Median cyst size was 30·0 mm (mean 31·5 mm, SD 10·9 mm).

A polycystic appearance of the ovaries was not seen in any of the study or control cycles, despite the tendency to high LH concentrations observed in the infertile women with PPS profiles.

Discussion

This study analysed ovarian function in women with spontaneous normal menstrual cycles and unexplained infertility. A high proportion (29%) of these women demonstrated subnormal early luteal phase progesterone profiles, defined as PPS.

Statistical analysis of the PPS cycles, as defined, is complex. If individual plasma progesterone concentrations on days +1 to +5 are independent of each other then the expected frequency of PPS in the normal population would be of the order of 5%. Since it is likely that plasma progesterone concentrations on the individual days during this period are interrelated to some degree, the proportion of 'normal' cycles expected in the PPS group would be nearer to, but no greater than, 16%. This is the proportion of individual women expected to have concentrations >1 SD below the normal mean. There-

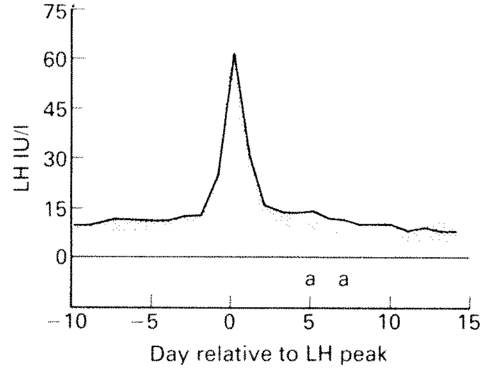

Fig. 5. Median plasma luteinizing hormone (LH) concentrations (IU/l) (days −10 to +14) in poor progesterone surge (PPS) cycles ($n = 51$). Shaded area represents the 95% confidence limits of the control population ($n = 43$). Significance (Wilcoxon rank sum test): a = $P<0{\cdot}02$.

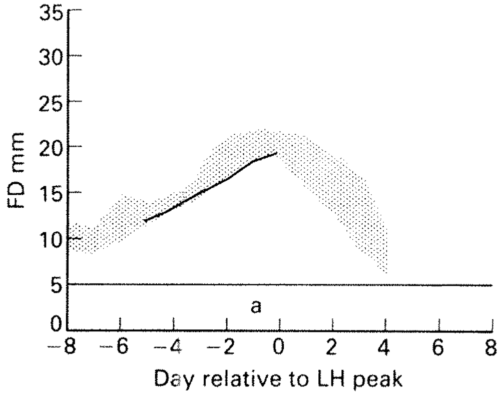

Fig. 6. Median follicular diameters (FD) (days −5 to 0) in poor progesterone surge (PPS) cycles ($n = 51$). Shaded area represents the 95% confidence limits of the control population ($n = 43$). Significance (Wilcoxon rank sum test): a = $P<0{\cdot}01$.

fore a minimum of half the women with PPS could not be accounted for by random events, and a direct relation between the PPS profile and infertility is likely to exist.

Further evidence of ovarian pathology in cycles with PPS was provided by the observation of other associated abnormalities such as luteal cyst formation, a pattern of follicular dynamics not seen in any of the control cycles. In the follicular phases preceding the PPS, high plasma concentrations of FSH and reduced concentrations of E2 were observed. Taken together, these results suggest that the PPS occurs after abnormal follicular metabolism, not solely as an abnormality generated at or after the onset of luteinization.

Previous studies, on smaller series, have suggested a role for diminished follicular phase gonadotrophic stimulation in the genesis of the deficient luteal phase (Sherman & Korenman 1974; McNatty *et al.* 1975a; Stouffer & Hodgen 1980; Aksel 1980; Di Zerega & Hodgen 1981; Gautray *et al.* 1981; Cook *et al.* 1983). This was not the case in the large series of PPS cycles reported here. It is well recognized that FSH is the stimulus to the antral follicle's proliferation of granulosa cells (McNatty *et al.* 1975b; Breitenecker *et al.* 1978; Marut *et al.* 1983), leading to the eventual dominance of a single follicle from which most of the circulating E2 is produced (Baird & Fraser 1974). Although the follicular growth profiles in the PPS cycles did not differ markedly from normal, the E2 and FSH data suggest that the dominant follicles recruited in these cycles could have been abnormal, providing less negative feedback suppression of FSH. This combination, which was in many cases associated with luteal cyst formation, preceded luteal phase endocrine dysfunction.

The high luteal phase FSH concentrations observed in the PPS cycles were not associated with reduced E2 concentrations and may be a consequence of differences in the secretion of inhibin-like products by these abnormal corpora lutea (McLachlan *et al.* 1987). This will be an interesting area of study in the future.

To date, the significance, if any, of an association between subnormal luteal phase plasma progesterone concentrations with infertility, while frequently recorded, has been difficult to assess. The combined endocrine and ultrasound data presented here provide three clues in addressing this problem.

In almost half of the PPS cycles ultrasound evidence of luteal cyst formation was seen. In 18 of 23 (78%) instances follicular shrinkage was not observed following the LH peak, suggesting that these follicles had failed to ovulate. Oocyte entrapment (Aksel 1987) could account for infertility in these cycles. A high incidence of cycles demonstrating luteinized unruptured follicles (LUF) was reported, in a population of women with unexplained infertility (Koninckx *et al.* 1978). These cycles were characterized by a delay in the onset of luteinization as assessed by elevation in basal body temperature. Similar patterns were subsequently seen in patients with endometriosis, who were also found to exhibit subnormal progesterone profiles in the early luteal phase (Brosens *et al.* 1978). The ultrasound and endocrine profiles in the present study lend support to the hypothesis that the LUF syndrome accounts for infertility in many cycles associated with impaired luteal phase steroidogenesis.

Secondly, high FSH and low E2 plasma concentrations seen in the follicular phase of the PPS cycles may, in addition to luteal cyst formation, also be a marker for abnormal follicular metabolism in these cycles. Primate studies (Marut *et al.* 1983) revealed that pre-ovulatory follicles from which granulosa cells were removed evolved dysfunctional corpora lutea, characterised by decreased progesterone secretion. It was concluded that granulosa lutein cells were the predominant source of luteal phase progesterone. It was noted in these studies that luteal phase E2 production remained normal suggesting that E2 in these cycles derived principally from luteinized theca cells. This concept of differing cellular pathways of E2 and progesterone production by the corpus luteum would be in accordance with the observations of Macnaughton *et al.* (1981), and could explain the observation of normal luteal phase E2 concentrations in cycles with deficient progesterone output. If PPS cycles were a result of a reduced granulosa celll population or a reduced degree of luteinization of the granulosa cells, such disturbances in the follicular micro-environment, in addition to being associated with abnormal hormone profiles, could directly compromise oocyte quality, with consequent implications for fertility.

Thirdly, it is possible that reduced early luteal phase circulating concentrations of progesterone, might adversely affect endometrial receptivity to an implanting blastocyst (Wentz 1982;

Kusuda *et al.* 1983). As well as reducing fecundity this could have profound implications for the successful continuation of pregnancy beyond the first few weeks of gestation (Soules *et al.* 1977; Tho *et al.* 1979; Annos *et al.* 1980).

In conclusion, subnormal profiles of early luteal phase plasma progesterone concentrations occurred frequently in patients with unexplained infertility. These cycles also demonstrated reduced E2 and increased FSH concentrations in the follicular phase, and a high occurrence of luteal cyst formation. The disturbed endocrine and ultrasound profiles reflected abnormal follicular/luteal metabolism and are in some cases probably a manifestation of the LUF syndrome. Further, it is highly unlikely that single (Israel *et al.* 1972; Shepard *et al.* 1977; Hull *et al.* 1982; Abdulla *et al.* 1983) or limited multiple (Abraham *et al.* 1974) sampling techniques for measuring progesterone in the luteal phase will reliably detect abnormal cycles, as defined here, and unless ultrasound examination of follicular dynamics complements endocrine investigation, ovarian function cannot be considered to have been adequately assessed.

Acknowledgments

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A quantitative study of endometrial development in the luteal phase: comparison between women with unexplained infertility and normal fertility

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Summary. This study compared endometrial development in the luteal phase of women with unexplained infertility ($n = 30$) with that in women with normal fertility ($n = 70$) by the use of quantitative histological techniques (morphometric analysis) on endometrial specimens which were precisely timed from the luteinizing hormone surge. When overall endometrial development (histological dating) was considered, the proportion of women with unexplained infertility who had retarded endometrial development (20%) was found to be significantly higher than for women with normal fertility (3%) ($P<0{\cdot}01$). When individual histological features were considered, women with unexplained infertility were found to have significant deviation from the normal range established from fertile women in only five of the 14 histological features measured. All of these five features related to the glandular but not to the stromal component of the endometrium; four of these five features are related to glandular secretory activity.

It has been recognized for almost 40 years that abnormal (retarded) endometrial development in the luteal phase is one of the causes of infertility and this has also been used as the basis for the diagnosis of the clinical entity 'luteal phase defect' (Jones 1949; Jones 1977). However, the frequency of this condition is still a matter of debate. Using the histological criteria of Noyes *et al.* (1950) to date endometrium, the frequency of retarded endometrium among women with infertility has been reported to vary from 8 to 65% (Rosenberg *et al.* 1980; Wentz 1980; Downs & Gibson 1983; Witten & Martin 1985; Huang 1986; Balasch *et al.* 1982; Cook *et al.* 1983; Cumming *et al.* 1985). Such a large variation in the reported frequency of retarded endometrial development may be due to a number of reasons: but particularly to error in chronological dating, especially when the onset of the next menstrual period is used (Li *et al.* 1987), and to error in histological dating, particularly when the subjective dating criteria of Noyes *et al.* (1950) are used.

Recently, the precision of these traditional criteria has been analysed by Li *et al.* (1989a) who found that intra-observer variability alone could lead to 18% of false positive results (out-of-phase endometrium).

In this study, the aim was to examine endometrial development in the luteal phase in a group of women whose infertility was unexplained, using the improved, rigorous

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approaches as follows: (1) the use of the luteinizing hormone (LH) surge, rather than the next menstrual period, to time endometrial biopsy; (2) the use of morphometry for dating of overall histological development and analysis of individual histological features; (3) comparison with a control population with normal fertility.

Subject and methods

In this study, both fertile and infertile women were recruited from the gynaecological outpatient clinic of the University Department, Jessop Hospital for Women, Sheffield, during the years 1986 and 1987.

A consecutive series of 30 women whose infertility was found to be unexplained were studied. Infertility was considered unexplained if it was of more than one year's duration and no cause could be found on routine clinical investigation. For the latter there had to be normal, regular sexual intercourse, no ejaculatory problem, a normal semen analysis as defined by the World Health Organization (Belsey *et al.* 1980); normal regular menstrual cycles of between 25 and 35 days; the presence of one or more objective criteria of ovulation; normal thyroid function tests and plasma prolactin concentration and normal laparoscopic findings.

A total of 70 normal fertile women were included in this study. This group of subjects has been described previously (Li *et al.* 1988a).

Endometrial biopsy

Endometrial biopsy was performed as an outpatient procedure by the use of a Sherman's curette (Down's Surgical Ltd, Sheffield). This technique and that of the subsequent processing of the specimens have been described elsewhere (Li *et al.* 1988a).

All the biopsies were timed from the luteinizing hormone (LH) surge. The day of the LH surge (designated LH+0) was determined by daily LH assays on specimens either of morning urine or of plasma, starting on day 9 of the menstrual cycle (Li *et al.* 1987).

Quantitative histological techniques (morphometric analysis) were used to analyse the endometrial specimens. These techniques have been described previously and validated (Li *et al.* 1988a).

Salivary progesterone

In 63 women (24 with unexplained infertility, 39 with normal fertility), daily samples of saliva were obtained throughout the luteal phase. Progesterone concentration in the saliva was determined by a direct radioimmunoassay as described previously (Li *et al.* 1989b). For each day of the luteal phase, a cumulative salivary progesterone concentration was derived by summing up the daily progesterone concentration from day LH+1 to that particular day. The cumulative progesterone profile was defined as normal if it was >5th centile of those ($n = 55$) associated with normal endometrial development, as assessed by morphometric analysis (Li *et al.* 1988a).

Statistical aspects

The normal range of morphological features throughout the luteal phase was derived from the reference range (mean±1·96 SD) of the normal, fertile population ($n = 70$) (Li *et al.* 1988a). For each morphometric measurement, as 30 individual results were compared with the nomogram, it was possible that 5% (1·5) might fall outside the normal range by chance alone. With the Poisson distribution for rare events (Murdock and Barnes, 1980), it was calculated that the chance of 5 or more of the 30 results to fall outside the normal range in normal subjects was <0·019%. Therefore 5 or more of the 30 results outside the normal range would represent a significant deviation from normal and the population under consideration (unexplained infertility) would be likely to differ from the normal population in that respect.

The nonparametric Mann-Whitney U test was used to compare the results of endometrial dating between women with normal fertility and unexplained infertility. The two sample t test on log transformed data was used to compare the results of cumulative progesterone profiles between two groups of subjects. In the latter analysis, as multiple ($n = 11$) comparisons were made, the P value was considered to be significant only if it was <0·01.

Results

The mean age of the 70 women with normal fertility was 33·0 years (SD 4·1, range 22–40) whereas the mean age of the 30 women with unexplained infertility was 33·7 years (SD 4·6, range 22–44). The mean duration of infertility in the latter group was 6·2 years (SD 3·2, range 2–18).

Overall histological development (histological dating)

The median endometrial dating (defined as histological dating by morphometric analysis (in days) minus chronological dating by LH surge (in days)) in women with normal fertility ($n = 70$) was found to be −0·1 days (range −3·2 to 1·9); whereas the median endometrial dating in women with unexplained infertility ($n = 30$) was found to be −0·9 days (range −6·0 to 2·2). Using a Mann-Whitney *U* test to compare these two populations, the difference was found to be significant ($z = 2{\cdot}8$, $P<0{\cdot}01$).

The normal reference range of the results of endometrial dating, established from the normal fertile population mentioned above ($n = 70$) was −1·8 to +1·6 days (Li *et al.* 1988a; Li *et al* 1989b). Thus, retarded endometrial development could be defined as histological dating more than 1·8 days behind chronological dating, and advanced endometrial development as histological dating more than 1·6 days ahead of chronological dating. Using this definition, it was found that 2 of the 70 fertile women (3%) had retarded endometrial development, whereas 6 of the 30 women with unexplained infertility (20%) had retarded endometrial development. The difference between the two groups was statistically significant ($\chi^2 = 8{\cdot}4$, $P<0{\cdot}01$).

Individual histological features

The results of each of the 14 individual histological features measured by morphometric techniques are shown in Fig. 1. For each individual histological feature, the results of the 30 infertile subjects are shown on a background of the reference range derived from the normal fertile population ($n = 70$). It was found that in the 30 women with unexplained infertility, a statistically significant number (≥5) were outside the normal range in the following five histological features: (1) amount of secretion in gland lumen; (2) volume fraction of gland occupied by gland cell; (3) volume fraction of gland cell occupied by nucleus; (4) number of subnuclear vacuoles per 100 gland cells, and (5) amount of pseudostratification of gland cell. For the remaining nine histological features, the number of subjects who were outside the normal range was not statistically significant (4 or less out of 30).

Salivary progesterone profiles

Figure 2 illustrates the results of cumulative salivary progesterone profiles in those with normal fertility ($n = 39$) and those with unexplained infertility ($n = 24$). Significant difference ($P<0{\cdot}01$) between the two groups was observed on days LH+3 and LH+4, but not on other days. For comparison, the results of cumulative salivary progesterone profiles between those with normal ($n = 55$) and retarded ($n = 8$) endometrial development are shown in Fig. 2b. In this case, a significant difference ($P<0{\cdot}01$) between the two groups was observed on days LH+4 and LH+5.

The results of individual cumulative salivary progesterone profile of the eight subjects with retarded endometrial development are shown in Fig. 3.

Discussion

Although there have been several reports on the frequency of retarded endometrial development in the infertile population, most of them were poorly controlled (Rosenberg *et al.* 1980; Wentz *et al.* 1980; Mansuwan *et al.* 1982; Downs & Gibson, 1983; Witten & Martin, 1985; Cumming *et al.* 1985; Huang, 1986). A controlled study was reported by Balasch *et al.* (1986) who could not demonstrate any significant difference in the occurrence of retarded endometrial development (luteal phase defect) between an infertile population and a control fertile population. In that study, however, the infertile population was not clearly defined, the control fertile population was small ($n = 25$), and the dating of endometrium was performed by the traditional criteria of Noyes *et al.* (1950), the precision of which has recently been challenged (Li *et al.* 1989a; Li *et al.* 1989b). In contrast, our study used quantitative and more objective histological techniques (morphometric analysis) on endometrial biopsies which were all precisely timed by the LH surge, and showed, for the first time, a significant difference in the frequency of retarded endometrial development between a fertile and a well defined infertile population.

Individual histological features

In this study, the use of quantitatve histological techniques (morphometric analysis) enabled not only an overall assessment of endometrial development, but also the analysis of various individual histological features. In two previous studies (Li *et al.* 1988a; Li *et al.* 1988b) we

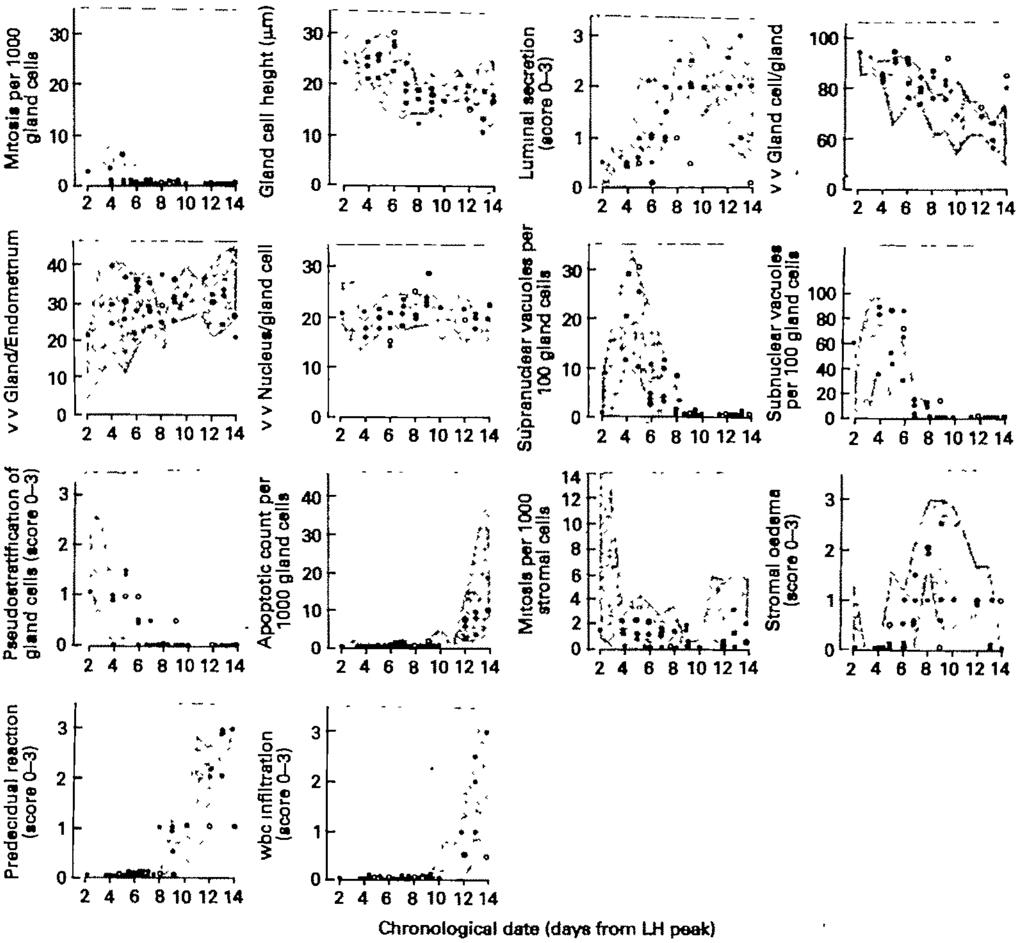

Fig. 1. Endometrial morphology in women with unexplained infertility ($n = 30$). The results of each individual morphometric measurement are shown on a background of the normal range established from a fertile population ($n = 70$). ●, overall endometrial development (histological dating) is normal, ○, overall endometrial development is retarded; vv, volume fraction of; wbc, white blood cell.

measured 17 histological features in each endometrial specimen. Of these, the glandular diameter was found to have a strong correlation with the volume fraction of the gland occupied by the gland cell ($r = 0{\cdot}86$, $P<0{\cdot}0001$) and therefore does not offer much additional information to the latter measurement; the measurements on venule diameter and the amount of extravasation had, on the other hand, relatively large variability which, in turn, may be due to a varying degree of tissue trauma sustained at the time of endometrial biopsy. For these reasons, these three measurements were omitted in this study

In women with unexplained infertility, significant deviation from the normal range was observed in only five of the 14 histological features measured Furthermore, all these five histological features are related to the glandular component and none to the stromal component of the endometrium; four of these five histological features are closely related to the secretory activity of the gland cells: the amount of secretion in gland lumen, the volume fraction of gland occupied by gland cell, the number of subnuclear vacuoles per 100 gland cells and the amount of pseudostratification of gland cell. It is possible that with the impairment of the secretory activity, the secretory materials are retained in the gland cells for a longer period of time, leading to the persistence of subnuclear vacuoles; at the same time, with the reduction in the amount of secretion delivered to the gland lumen, the gland lumen becomes less distended and so the volume fraction of gland occupied by

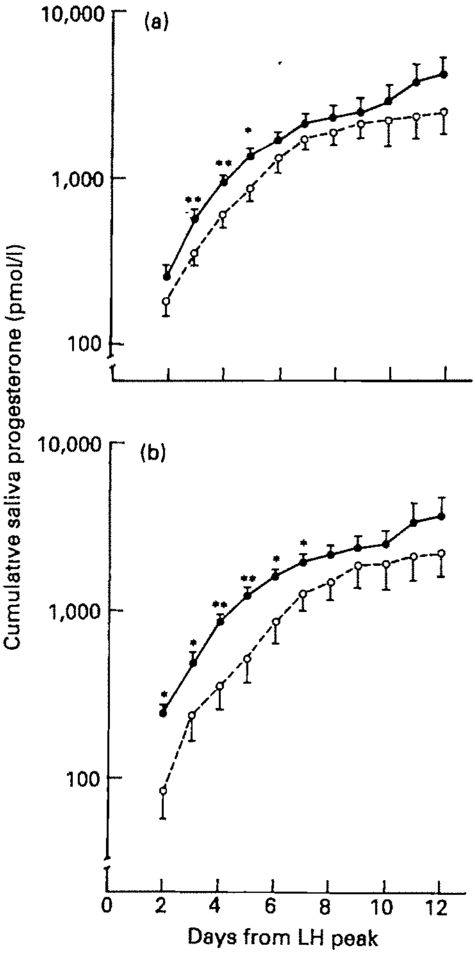

Fig. 2. The results (geometric mean with SE in vertical bar) of cumulative salivary progesterone profile (for definition, see text) of 63 women. (a) Comparison between those with normal fertility (●, $n = 39$) and unexplained infertility (○, $n = 24$) (b) Comparison between those with normal endometrial development (●, $n = 55$) and retarded endometrial development (○, $n = 8$). $^{*}P<0{\cdot}05$; $^{**}P<0{\cdot}01$.

gland cell is increased; and with the relative lack of secretory material distending the lumen, gland cells are more closely packed and appear more pseudostratified.

The remaining histological feature in which significant deviation from the normal range occurred in women with unexplained infertility was the volume fraction of gland cell occupied by the nucleus. In contrast to the above four features in which the majority of deviations (measurements falling outside the normal range) occurred in one particular direction (e.g. for volume fraction of gland occupied by gland cell, all the eight deviations were above the normal range and none was below the normal range), of the seven deviations, four were above and three below the normal range. The exact reason for this is unclear. All the deviations below the normal range occurred on day LH+6, which could well be accounted for by the persistence of sub-nuclear vacuoles, resulting in an increase in the volume of cytoplasm and corresponding decrease in the relative volume of cell nucleus. On the other hand, the reason for the remaining four deviations being above the normal range could be due to an increase in the volume of the nucleus, or a reduction in the volume of cytoplasm, or both. It is not possible from this study to deduce which is the more likely possibility, but refined methods of measurement on absolute nuclear volume will be required (Gunderson, 1986) to answer this question.

The other nine measurements, which are related to glandular mitotic activity, glandular degenerative change (apoptotic count), stromal mitotic activity, stromal vascular changes (oedema and neutrophil infiltration) and the predecidual reaction, did not appear to deviate from the normal in women with unexplained infertility.

Whereas the former five histological features are likely to reflect abnormal endometrial development in women with unexplained infer-

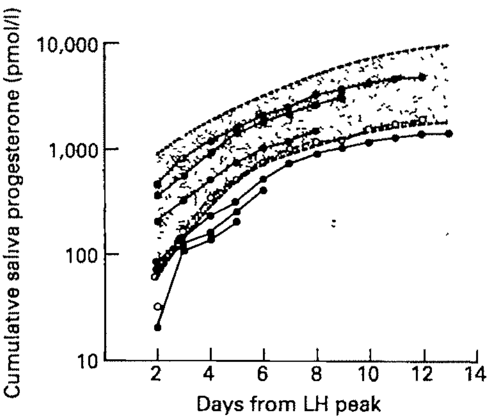

Fig. 3. Individual cumulative salivary progesterone profiles in subjects (6 with unexplained infertility, ●; 2 with normal fertility, ○) in whom endometrial development was retarded. The shaded area represents the normal range (5th to 95th centile) of cumulative salivary progesterone profile derived from 55 women in whom endometrial development was normal according to morphometric analysis.

tility, the latter nine histological features have little discriminating value between the endometrial development of fertile and infertile women. Further work, involving the use of quantitative electron-microscopy and immunocytochemistry, is currently in progress in our departments to elucidate the ultrastructural and histochemical differences in the glandular component (with an emphasis on the secretory activity) of the endometrium of normal fertile women and of women with unexplained infertility. Our data so far suggest that both the synthesis and secretion of an oligosaccharide epitope produced by endometrial gland cells (Smith *et al.* 1989) are reduced in women with unexplained infertility (Smith, personal communication).

Relation with progesterone profile

With respect to the relation between daily salivary progesterone profile, this study may be considered to be an extension of the one recently published (Li *et al.* 1989b). In addition, the salivary progesterone profiles of women with unexplained infertility were found to be significantly lower than those with normal fertility on days LH+3 and LH+4 (Fig. 2a). This suggests that suboptimal progesterone production by the corpus luteum may be responsible for abnormal endometrial development in women with unexplained infertility. However, further analysis of individual progesterone profiles of those with retarded endometrial development (Fig. 3) revealed half of them were associated with progesterone profile in the normal range. The overall conclusion, therefore, is that abnormal endometrial development in women with unexplained infertility is not always due to abnormal corpus luteum function but may instead be a result of an abnormal endometrial response. A progesterone receptor deficiency (Cooke and Lambadarios, 1974; Keller *et al.* 1979) is a possibility.

Comparison with endometrial development following progesterone receptor blockade

The endometrial development in the luteal phase of women with unexplained infertility may be compared to those induced by progesterone receptor blockade (Li *et al.* 1988b). In both situations, the overall endometrial development and glandular secretory activity were retarded, and in both the glandular mitotic activity and stromal predecidual reaction were not affected. However, progesterone receptor blockade by mifepristone alone resulted in a significant increase in the amount of glandular degenerative changes (apoptotic count) and stromal leucocytic infiltration, and significant reduction in stromal oedema. These changes were not observed in women with unexplained infertility. It appears, therefore, while they share a number of features in common, there are distinct differences between the two.

Conclusions

The finding in this study that retarded endometrial development occurs in 20% of women with unexplained infertility suggests that abnormal endometrial development could be an important underlying cause of this clinical entity and that further research into the endometrium, using improved techniques, such as those described in this study, should be considered. However, proof that retarded endometrial development is a direct cause of infertility requires the demonstration that therapy that corrects the defective endometrial development restores normal fertility.

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Uterine size and endometrial thickness and the significance of cystic ovaries in women with pelvic pain due to congestion

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Summary. In a group of 55 women with chronic pain due to pelvic congestion measurement by ultrasound revealed they had a larger uterus and thicker endometrium as compared with a group of normal women matched for age, parity and the presence of polycystic ovaries found on ultrasound scanning. Many women with pelvic congestion (56%) were found on ultrasound to have cystic changes in their ovaries which ranged from a classic polycystic pattern to the appearance of clusters of 4–6 cysts in bilaterally enlarged ovaries. It is suggested that uterine enlargement and thickening of the endometrium are caused by oestrogen, either from the effects on the target organs of an increased concentration or of hypersensitivity to oestrogen.

It has been shown by pelvic venography that more than 80% of women, without an obvious cause for their pain at laparoscopy, have marked venous congestion in the major pelvic veins, which are frequently dilated up to three times their normal diameter (Beard *et al.* 1984). Further studies (Reginald *et al.* 1987) using the specific venoconstrictor, dihydroergotamine, administered intravenously to women during an acute attack of pain, have shown that narrowing of the veins occurs with improvement of the congestion and a significant reduction in pain. These findings suggest that venous congestion in the pelvis is a common cause of pain in women which can be temporarily diminished by venoconstriction resulting in an improvement in venous blood flow. Indirect evidence from these and other studies suggests that ovarian hormones are responsible for the state of chronic pelvic congestion (Taylor 1949c; Reginald *et al.* 1987; Farquhar *et al.* 1989) but, as yet, direct evidence for this is lacking.

It is hypothesized that if ovarian hormones are implicated in the mechanism of pelvic congestion, given its chronic nature, hypertrophy will occur in target organs such as the uterus and endometrium and that the ovaries of these women will also show structural abnormalities. The purpose of this study was to investigate these possibilities.

Patients and methods

Pelvic ultrasound scans were done on 55 women

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who, having been investigated for pelvic pain, had been found to have pelvic congestion with a venogram score of ≥5 (Beard *et al.* 1984). All of them had had a laparoscopy at which no obvious pathology had been found. The women in the study group were compared with 65 women selected from a group who had taken part in a previous study of normal women in which the same ultrasonographer (J.A.) had taken part (Polson *et al.* 1988). The women in the comparison group were selected to ensure that their age distribution, parity and the presence or absence of polycystic ovaries (PCO) on ultrasound were similar to those of the patient group. The inclusion of PCO on ultrasound as a matching characteristic was dictated by the finding of Polson *et al.* (1988) that it is associated with uterine enlargement. Table 1 shows the distribution of matching characteristics between the study and comparison groups. It was recognized that for ethical reasons it would not be possible to perform a pelvic venogram on women in a control group but the finding by Beard *et al.* (1984) that normal women rarely have a venogram score ≥5 largely overcomes this deficiency.

Ultrasound scanning

Pelvic ultrasound scans were performed by one of the authors (JA) with no prior knowledge of the results of other investigations. An Aloka sector scanner (SSD 720) was used with a 3·5 mHz long-focused transducer with all scans being recorded on video tape. The ovaries were identified and measured in three planes and the volume calculated (in cm^3) (Sample *et al.* 1977). When a dominant follicle was observed on the scan, measurements were taken from the contralateral ovary. Ovarian morphology was described in terms of volume and the number, size and distribution of cysts within the stroma (Adams *et al.* 1985). The uterus was measured in the sagittal plane and cross sectional area was calculated from the product of the maximal length from fundus to cervix and maximum depth (Adams *et al.* 1985). The endometrial echo was identified (Fleischer *et al.* 1986) and maximum thickness of the endometrium was measured at the level of maximum depth of the uterus.

Table 1. Characteristics of women in the study and comparison groups

	Pelvic congestion group (n=55)		Comparison group (n=65)	
Age (years) range	19–44		18–42	
Parous	37	(67%)	40	(62%)
Nulliparous	18	(33%)	25	(38%)
UPCO	31	(56%)	29	(45%)

UPCO = Ultrasound Polycystic Ovary.

Statistical analysis

The main objective of the study was to determine whether ovarian volume, uterine area and endometrial thickness were increased in women with pelvic congestion compared with those without pelvic congestion. Analysis of variance was used to assess the significance of the association of pelvic congestion with endometrial and uterine hypertrophy and ovarian enlargement after allowing for the effects of possible confounding variables such as PCO on ultrasound, parity and day of the cycle. The significance of the interactions between the main effects was assessed on each analysis. The results are presented as means and standard deviation for the pelvic congestion group and the comparison group. We also calculated the 95% CI for the difference between means.

Results

The mean values and significance of differences between groups for ovarian volume, uterine area and endometrial thickness are shown in Tables 2, 3 and 4.

Ovarian appearances

Of the 55 women with pelvic congestion 31 (56%) were found to have PCO on ultrasound. The number and distribution of the cysts ranged from a classic polycystic appearance (Adams *et al.* 1985; Polson *et al.* 1988) to the presence of clusters of four to six cysts 5–15 mm in diameter in bilaterally enlarged ovaries. Table 2 shows that from the analysis of variance there is no significant difference in ovarian volume between women in the pelvic congestion and the comparison group. Those women with PCO on ultrasound have a significantly greater ovarian volume than those without. There was a significant interaction between PCO on ultrasound and pelvic congestion (P<0·02) which indicates a larger discrepancy in ovarian volume between

Table 2. Comparison of ovarian volume in ovaries with and without cystic changes on ultrasound scan in pelvic congestion and comparison groups

	Ovarian volume (cm³)							
	Cystic ovaries			Normal ovaries				
Study group	*n*	mean	(SD)	*n*	mean	(SD)	Difference between means (95% CI)	
Pelvic congestion	31	12·5	(3·8)	24	6·8	(1·6)	5·7	(4·7–6·6)
Comparison group	29	14·5	(3·5)	36	6·2	(1·4)	8·3	(7·3–9·2)

CI = confidence interval.

cystic and non-cystic ovaries in the comparison group than in those women with pelvic congestion.

Uterine cross-sectional area

Fig. 1 shows a tranverse section of a uterus on ultrasound with the uterine cavity in the centre. Dilated pelvic veins are shown to the right of the uterus. Table 3 shows from analysis of variance that women with pelvic congestion have a uterine cross sectional area significantly greater than those in the comparison group ($P<0{\cdot}001$). There were no significant interactions with respect to uterine area between parity, PCO on ultrasound and pelvic congestion. In other words, women with pelvic congestion had a greater uterine cross sectional area than those of the comparison group that was independent of parity and the presence of PCO on ultrasound. The uterine area was not analysed relative to the phase of the menstrual cycle as, unlike the endometrium, it did not appear to vary significantly during the cycle (McCarthy *et al.* 1986).

Endometrial thickness

Only data obtained from women with regular cycles could be included in the analysis of endometrial thickness. For this reason all women with ultrasound PCO, both in the pelvic congestion and comparison groups, were excluded because most of them had irregular cycles. Endometrial thickness was compared between 24 women in the pelvic congestion group with normal ovaries on ultrasound and 33 women in the control group also with normal ovaries. For analysis of variance, the measurements of endometrial thickness were grouped according to the phase of the cycle in which they were obtained (Table 4). Endometrial thickness was found to be significantly greater in those with pelvic congestion than in the comparison group (11·7 mm compared with 8·3 mm, $P<0{\cdot}0001$), and to change significantly with the phase of the menstrual cycle ($P<0{\cdot}001$). These effects were independent as there was no significant interaction between pelvic congestion and day of cycle with respect to endometrial thickness.

Discussion

The present findings add further evidence of widespread physical changes in the pelvic organs of women with pelvic congestion. They also confirm the observations by Taylor (1949a and b) that pelvic congestion is associated with enlargement of the uterus, thickening of the endometrium and cystic change in the ovary in most of these women. While the uterine enlargement may occur simply as a result of engorgement of uterine veins, it seems more likely that myometrial hypertrophy is due to increased exposure to, or sensitivity to, oestrogen (Williams & Kinney, 1944; Selye *et al.* 1942; Polson *et al.* 1987). This view is further supported by the observation that pelvic pain with congestion is confined to the reproductive years of life (Gordienne & Lhoist, 1979; Beard *et al.* 1988).

The clinical features of the 56% of women with pelvic congestion with PCO on ultrasound

Table 3. Comparison of uterine area (cm²) in pelvic congestion and comparison groups

Study group	Uterine area (cm²) mean (SD)
Pelvic congestion (*n*=55)	39·1 (6·1)
Comparison group (*n*=65)	28·3 (6·2)
Difference between means	10·8
95% CI	9·0–12·6

CI = confidence interval.

Table 4. Comparison of endometrial thickness in pelvic congestion and comparison groups at various phases of the menstrual cycle

	Endometrial thickness (mm)							
	Pelvic congestion group			Comparison group				
Day of cycle	*n*	mean	(SD)	*n*	mean	(SD)	Difference between means (95% CI)	
1–9	4	7·7	(2·5)	4	5·2	(1·7)	2·5	(1·1–3·9)
10–14	9	11·5	(3·1)	12	7·5	(1·8)	4.0	(2·6–5·4)
15–22	5	13·4	(4·5)	9	10·1	(3·4)	3·3	(1·9–4·7)
≥23	6	13·0	(3·4)	8	8·8	(1·5)	4·2	(2·8–5·6)
All days	24	11·7	(308)	33	8·3	(2·7)	3·4	(2·0–4·8)

CI = confidence interval.

need to be distinguished from those of women with the classical polycystic ovary syndrome. None of the women with pelvic congestion and ultrasound PCO was hirsute or amenorrhoeic, although some had dysfunctional menstrual bleeding. The significance of the cystic changes in the ovary remain unclear. The ultrasound pattern of cysts was heterogeneous and, although some women had changes typical of polycystic ovaries, others had groups of larger cysts clustered in certain areas of the ovary. The fact that more than half of the women studied had structural abnormalities of the ovaries detectable on ultrasound suggests that these ovaries may, in some way, be dysfunctional. Thus is seems reasonable to propose that ovarian dysfunction may be causally related to the pathogenesis of venous congestion, although this does not provide an explanation for the congestion found in the women with apparently normal ovaries. The same dilemma is also present when considering the finding of uterine enlargement and endometrial thickening in women with pelvic congestion. There was no evidence of a relation between these changes and the presence of ultrasound PCO. All that can be said is that there is, as yet, an undetermined association between pelvic congestion and an increase in uterine and endometrial thickness in women with pelvic congestion which may be mediated through oestrogen.

Additional indirect evidence that ovarian hor-

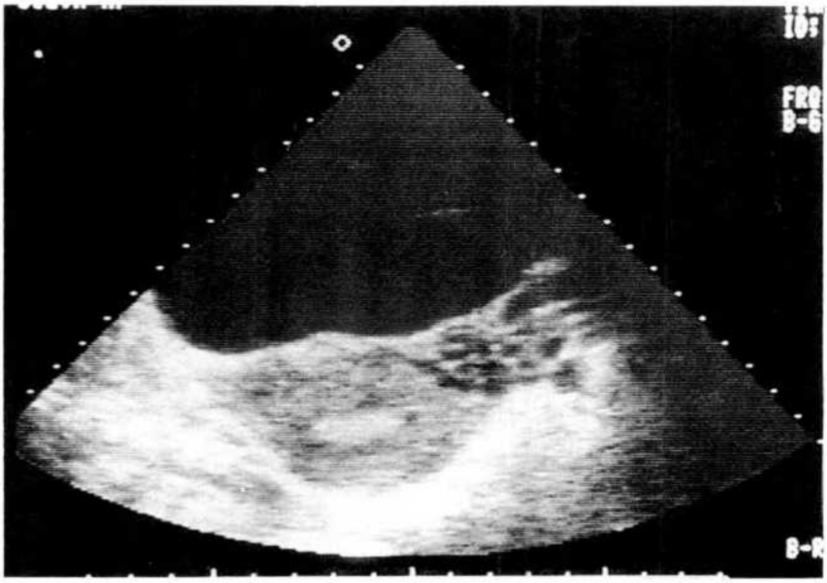

Fig. 1. Ultrasound scan showing transverse section of a uterus with the uterine cavity at the centre and dilated veins to the right of the uterus.

mones play a central role in the pathogenesis of pelvic congestion comes from the demonstration that suppression of ovarian activity with medroxyprogesterone acetate leads to contraction of dilated pelvic veins, reduction of congestion and relief of pelvic pain (Reginald *et al.* 1989; Farquhar *et al.* 1989). More evidence is needed of the ovarian function and hormonal status of women with pain due to pelvic congestion, in particular studies of the local concentration of ovarian hormones to which the uterus, endometrium and pelvic veins are exposed, before it is possible to clarify the aetiology of this condition further.

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Factors influencing the prevalence and severity of dysmenorrhoea in young women

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Summary. Factors influencing the prevalence and severity of dysmenorrhoea were assessed longitudinally in a representative sample of young women born in 1962. The prevalence of dysmenorrhoea was lower ($P<0{\cdot}01$) at 24 years of age than at 19 years of age. At 24 years of age, 67% of the women still experienced dysmenorrhoea; 10% reported dysmenorrhoea which limited daily activity. The severity of dysmenorrhoea (linear analogue scale) was lower ($P<0{\cdot}001$) at 24 years of age (3·4, SD 2·8) than at 19 years (4·1, SD 3·2). The prevalence and severity of dysmenorrhoea were reduced ($P<0{\cdot}05$) in women who were parous in 1986 and nulliparous in 1981; but was unchanged in women who were still nulliparous or women who had had a miscarriage or abortion. Dysmenorrhoea was reduced ($P<0{\cdot}001$) in oral contraceptive users. The severity of dysmenorrhoea was significantly associated with the duration of menstrual flow, menarcheal age and cigarette smoking. The severity of dysmenorrhoea was not associated with age as an isolated factor, nor with height, weight, length of menstrual cycle or frequency of physical exercise.

Primary dysmenorrhoea is a common gynaecological disorder which has been reported to be one of the greatest single causes of periodic absenteeism amongst young women (Carey 1975; Ylikorkala & Dawood 1978). Although it is generally accepted that dysmenorrhoea is common in young women, the reported prevalence has varied considerably (Morrison & Nicholls 1981; Lumsden 1985). A possible explanation for this large variation is that specific groups of women, such as students (Miller 1930; Svennerud 1959; Svanberg & Ulmsten 1981), teenagers and their mothers (Widholm & Kantero 1971), patients attending an outpatient clinic (Coppen & Kessel 1963; Pullon *et al.* 1988) and industrial workers (Bergsjö *et al.* 1975) have been studied.

In 1982 we reported our findings regarding the prevalence of dysmenorrhoea in a representative sample of 19-year-old women resident in the city of Goteborg (Andersch & Milsom 1982). Dysmenorrhoea was reported by 72% of the women. Dysmenorrhoea which limited daily activity and was unimproved by analgesic drugs was reported by 15%. In this cross-sectional study it was not possible to assess the influence of time related factors, such as increasing age and changes in parity on the prevalence and severity of dysmenorrhoea. As far as we are aware no longitudinal studies of dysmenorrhoea, based on a representative sample of the total population of women, have been published previously.

The aims of the present study were to investi-

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gate the prevalence and severity of dysmenorrhoea in the same women who participated in the assessment 5 years previously in 1981, and to assess possible factors influencing the prevalence and severity of dysmenorrhoea.

Subjects and methods

In 1981 we performed an epidemiological study of dysmenorrhoea among 19-year-old women resident in the city of Göteborg (Andersch & Milsom 1982). At that time there were 2621 women aged 19 years living in Göteborg. A sample of one in four of these women was obtained at random from the population register. The study population comprised 656 women who were invited by letter to co-operate in the investigation by completing and returning an enclosed questionnaire about dysmenorrhoea and related factors. The questionnaire was completed by 596 (90·9%) of the 656 women invited to participate in the investigation.

In 1986, an attempt was made to contact the same 596 women who returned the questionnaire sent out in 1981; addresses were available from the National Population Register for 589 of them, one woman had died and six had emigrated and no forwarding address was available. Of these 589 women, 453 women were still resident in the city of Göteborg.

The 589 women were invited by letter to co-operate in the investigation by completing and returning an enclosed questionnaire. If no reply was received, additional letters were sent 2 and 4 weeks after the first one. In the first run, 50% answered and after the first reminder 71% had answered. After the final inquiry a total of 489 (83%) had answered. The questionnaire included data regarding the duration and severity of menstrual pain, need for medical attention, ability to work during menstruation and menstrual pattern. Information was also obtained about contraception, parity and various sociobiological factors. The severity of dysmenorrhoea was assessed by the verbal multidimensional scoring system shown in Table 1 and by a linear analogue scale (Revill *et al.* 1976).

Table 1. The verbal multidimensional scoring system for the assessment of the severity of dysmenorrhoea

Grade of dysmenorrhoea	
0	Menstruation is not painful and daily activity is unaffected.
1	Menstruation is painful but seldom inhibits the woman's normal activity. Analgesics are seldom required. Mild pain.
2	Daily activity affected. Analgesics required and give relief so that absence from work or school is unusual. Moderate pain.
3	Activity clearly inhibited. Poor effect of analgesics. Somatic symptoms, e g. headache, tiredness, nausea, vomiting and diarrhoea Severe pain.

Characteristics of the respondents and non-respondents

As the population register includes some basic vital statistics for all the women in the sample, it was possible to compare the 100 non-respondents with the 489 respondents. There were no significant differences between respondents and non-respondents regarding marital status or foreign extraction and by definition all the women were born the same year (1962). Nor was there any significant difference between responders and non-responders regarding place of residence (i.e. resident/non-resident in Göteborg). There was no significant difference in the severity of dysmenorrhoea reported in 1981 between the responders and non responders to the 1986 questionnaire (linear analogue scale: 4·1 (SD 3·2); *vs* 4·4 (SD 3·2); verbal multi-dimensional scoring system: 2·2 (SD 1·0) *vs* 2·2 (SD 1·0). From the information available there were no indications that those who did not respond differed from the respondents.

Statistical methods

The results are given in the text as means (SD). Significance tests for correlation were performed with Pitman's permutation test, which is a non-parametric trend test applicable to discrete as well as continuous distributions (Bradley 1968). With the use of Pitman's permutation test the four grades of dysmenorrhoea were included together in the calculations, and not each grade separately. In the analyses attention was paid to the influence of background variables by dividing the women into subgroups according to relevant background variables. Correlation analysis with Pitman's permutation

Table 2. Dysmenorrhoea ranked in order of prevalence and severity in the same population ($n = 460$) assessed in 1981 and 1986 by the verbal multidimensional scoring system

Grade of dysmenorrhoea	Grade of dysmenorrhoea 0	1	2	3	Total 1986 n (%)
0	72	60	13	8	153 (33)
1	37	69	39	17	162 (35)
2	15	28	40	17	100 (22)
3	3	5	12	25	45 (10)
Total 1981 n (%)	127 (28)	162 (35)	104 (23)	67 (15)	

Linear non-parametric permutation test. $P<0\cdot05$ = significant. Significance of difference between 1981 and 1986: $P<0\cdot01$.

test was performed within each subgroup. The results from the subgroups were then pooled and tests of significance were performed over groups according to a procedure described by Mantel (1963). A linear non-parametric test was used for comparison of paired data (Bradley 1968).

Results

The questionnaire was completed by 489 (83%) of the 589 women invited to participate in this investigation. The 489 respondents represent 75% of the original 656 women invited in 1981 to take part in the first phase of this longitudinal investigation.

Prevalence

The prevalence of dysmenorrhoea in 1986 when the women were 24 years old was 67% which was lower ($P<0\cdot01$) than the 72% reported by the same women 5 years earlier (Table 2). The proportion of women with severe dysmenorrhoea which limited daily activity and was unimproved by analgesics had decreased from 15% in 1981 to 10% in 1986.

Severity

An intra-individual comparison of the severity of dysmenorrhoea, assessed on both occasions by the linear analogue scale, is shown in Fig. 1. At the assessment in 1986, 254 individuals had a lower linear analogue scale value compared with 1981, 19 had the same value on both occasions and 199 reported a higher value in 1986 compared with 1981. The mean linear analogue scale value for the responders in 1981 was 4·1 (SD 3·2) compared with 3·4 (SD 2·8) for 1986 ($P<0\cdot001$).

Contraception

As contraceptive methods may affect the prevalence and severity of dysmenorrhoea, the respondents were divided into three groups: oral contraceptive (OC) users, intrauterine contraceptive device (IUCD) users and non-users of either OC or an IUCD. In the statistical analysis attention was paid to pregnancy history as a background factor (Table 3). The prevalence and severity of dysmenorrhoea were significantly reduced in OC-users compared with IUCD users ($P<0\cdot05$), or non-users of OC or an IUCD ($P<0\cdot001$). There was no significant difference in the prevalence and severity of dys-

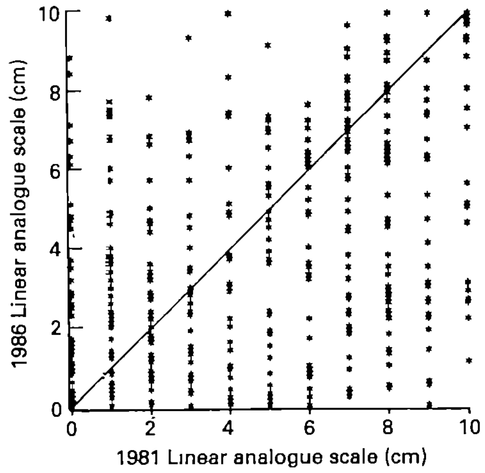

Fig. 1. An intra-individual comparison of the severity of dysmenorrhoea in the same population of women assessed when 19 and 24 years old by a linear analogue scale ($n = 472$). The severity of dysmenorrhoea was reduced ($P<0\cdot001$) at 24 years of age.

Table 3. Prevalence and severity of dysmenorrhoea related to the method of contraception Parity was included as a background variable in this analysis

	Grade of dysmenorrhoea			
	0 *n* (%)	1 *n* (%)	2 *n* (%)	3 *n* (%)
OC-users	99 (40)	102 (41)	33 (13)	13 (5)
IUCD-users	13 (25)	18 (35)	18 (35)	3 (6)
Non-users of OC & IUCD	37 (26)	34 (24)	45 (31)	27 (19)

OC = oral contraception IUCD = intrauterine contraceptive device
Pitman's permutation test. $P<0.05$ = significant; NS = not significant. Significance of difference between: OC-users and IUCD-users, $P<0.05$; OC-users and non-users of OC & IUCD, $P<0.001$; IUCD-users and non-users of OC & IUCD, NS.

menorrhoea between IUCD-users and non-users of OC or an IUCD.

Parity

In 1981 the prevalence and severity of dysmenorrhoea reported by parous women was lower ($P<0.01$) than in women who had never been pregnant or women who had had an abortion or miscarriage. To assess further the influence of parity on the prevalence and severity of dysmenorrhoea, an individual-based, longitudinal analysis was performed utilizing the results from women who were nulliparous in 1981 (Table 4). The corresponding respondents in 1986 were divided into three groups; nulliparous women; parous women; and women who had not given birth to a child but who had been pregnant and the pregnancy had terminated in legal abortion or miscarriage. A significant reduction ($P<0.05$) in the prevalence and severity of dysmenorrhoea was recorded in women who were parous in 1986 but nulliparous in 1981. The prevalence and severity of dysmenorrhoea was unchanged in women who were nulliparous on both occasions and in women who were nulliparous in 1981 and had had an abortion or miscarriage since then.

Menarche

A significant ($P<0.01$) association was found between menarcheal age and the severity of dysmenorrhoea. Early menarche was related to an increase in the severity of dysmenorrhoea (Table 5).

Height and weight

The severity and prevalence of dysmenorrhoea were unaffected by the woman's height or weight (Table 5).

Table 4. The influence of parity on the prevalence and severity of dysmenorrhoea, analysed on an individual basis utilizing the results from 1981 and 1986 (Linear non-parametric permutation test)

			Grade of dysmenorrhoea			
	Year	Status	0 *n* (%)	1 *n* (%)	2 *n* (%)	3 *n* (%)
A	1981	Nulliparous	67 (27)	95 (39)	54 (22)	30 (12)
B	1986	Nulliparous	79 (32)	92 (37)	47 (19)	28 (11)
C	1981	Nulliparous	23 (34)	18 (27)	12 (18)	14 (21)
D	1986	Parous	27 (40)	21 (31)	13 (19)	6 (9)
E	1981	Nulliparous	14 (28)	12 (24)	15 (30)	9 (18)
F	1986	Abortion or miscarriage	11 (22)	17 (34)	18 (36)	4 (8)

Significance of difference between C and D: $P<0.05$
No significant difference between A and B, and E and F.

Table 5. The severity of dysmenorrhoea related to certain biological factors

	Grade of dysmenorrhoea			
Biological factors	0 *n* mean (SD)	1 *n* mean (SD)	2 *n* mean (SD)	3 *n* mean (SD)
Height (cm) NS	157 166·3 (5·6)	167 168·1 (5·7)	106 167·3 (6·0)	47 168·3 (5·3)
Weight (kg) NS	156 59·0 (9·0)	164 59·8 (6·9)	105 60·4 (8·0)	45 60·3 (9·5)
Age at menarche (years)*	154 13·1 (1·4)	162 12·9 (1·5)	100 12·8 (1·3)	46 12·6 (1·2)
Duration of menses (days)†	155 5·0 (1·2)	165 5·0 (1·1)	105 5·5 (1·1)	44 5·8 (1·8)
Length of cycle (days) NS	142 27·0 (3·6)	157 27·0 (4·0)	101 27·7 (3·8)	41 27·6 (4·8)

Correlation analysis according to Pitman's permutation test. NS = not significant; * = $P<0·01$; † = $P<0·001$.

Menstrual cycle and menstruation

The severity and prevalence of dysmenorrhoea were unaffected by the length of the menstrual cycle. There was, however, a significant ($P<0·001$) association between the severity of dysmenorrhoea and the duration of menstrual flow. The severity of dysmenorrhoea increased with increasing duration of menstruation (Table 5).

Smoking habits

A significant ($P<0·01$) association was found between the severity of dysmenorrhoea and cigarette smoking. The severity of dysmenorrhoea was increased in smokers compared with non-smokers (Table 6) and increased significantly ($P<0·01$) with the number of cigarettes smoked per day.

Physical exercise

There was no association between the prevalence and severity of dysmenorrhoea and the frequency of physical exercise.

Medical requirements

At the assessment in 1986, 33% of the women with dysmenorrhoea regularly consumed analgesics for the treatment of dysmenorrhoea compared with 38% in 1981. The use of OC for the treatment of dysmenorrhoea was largely unchanged (21% in 1981 and 22% in 1986). In 1986, 40 of the 70 women who used OC because of dysmenorrhoea also required analgesics during menstruation, compared with 71 of 89 women who used OC for dysmenorrhoea in 1981. In 1986, 59 respondents (18%) suffering from dysmenorrhoea reported that they had consulted a doctor for the treatment of dysmenorrhoea, while 19% desired medical attention for dysmenorrhoea.

Absenteeism

The frequency of absenteeism in 1986 was reduced ($P<0·001$) compared with 1981. At the assessment in 1986, 34% of the respondents reported absenteeism due to dysmenorrhoea compared with 51% in 1981. In 1986, absence due to dysmenorrhoea every menstruation was reported by 3% (1981: 8%) while 2% (1981: 6%) were absent every other menstruation. Occasional absenteeism due to dysmenorrhoea was reported by 30% of the respondents in 1986 compared with 37% in 1981. The inability to work was found to be highly associated ($P<0·001$) with the reported severity of dysmenorrhoea.

Discussion

The general consensus of present opinion, based on available cross-sectional studies, is that dysmenorrhoea occurs more often during the teenage years after the menarche and then less often

Table 6. The severity of dysmenorrhoea related to cigarette smoking

	Grade of dysmenorrhoea			
	0 *n* (%)	1 *n* (%)	2 *n* (%)	3 *n* (%)
Smokers	57 (29)	61 (31)	53 (27)	27 (14)
Non-Smokers	97 (36)	103 (38)	50 (19)	19 (7)

Pitman's permutation test. $P<0·05$ = significant Significance of difference between non-smokers and smokers: $P<0·01$.

in women after the age of 20-25 years (Widholm & Kantero 1971; Bergsjö 1975; Ylikorkala & Dawood 1978; Morrison & Nicholls 1981; Svanberg & Ulmsten 1981; Lumsden 1985; Pullon *et al.* 1988). However it remains unclear whether increasing age alone, as a separate factor, influences the occurrence of dysmenorrhoea. Other factors such as changes in parity and the use or non-use of contraception, are also time related, and may interfere with any assessment of age, as an isolated factor.

A longitudinal study of the prevalence and severity of dysmenorrhoea in a representative sample of young women has not to our knowledge been published previously. The Swedish Population Register, which provides up-to-date information on the population living in the country at any one time, is suitable for epidemiological studies because the register permits the selection of a representative group from the total population (Andersch & Milsom 1982). The results reported in the present study were obtained in the same individuals who were first assessed in 1981. The participation frequency in 1981 was 91%. In the present study it was possible to assess 489 (83%) of the 596 respondents from 1981. This represents 75% of the original 656 women invited 5 years earlier to take part in the first phase of this longitudinal investigation.

According to Ylikorkala & Dawood (1978) it is important to use multidimensional quantitation when assessing the pain associated with dysmenorrhoea. In the present study the severity of dysmenorrhoea was measured by a verbal multidimensional scoring system which grades the severity of pain and also takes into account the effect on daily activity, systematic symptoms and analgesic requirements. In addition the respondents assessed the severity of dysmenorrhoea with a linear analogue scale (Revill *et al.* 1976). There was a good correlation between the assessment of dysmenorrhoea by these two methods at both measuring points.

The prevalence of dysmenorrhoea in 1986, when the women were 24 years old, was found to be 67%, which is significantly lower than the 72% reported in 1981. However, it was obvious from our results that many women still experienced dysmenorrhoea in 1986, despite being 5 years older. The results were thus analysed in an attempt to identify those factors influencing the occurrence of dysmenorrhoea. Factors of possible importance for the prevalence and severity of dysmenorrhoea were analysed separately, taking into account relevant background factors.

The prevalence and severity of dysmenorrhoea was unchanged in women who were still nulliparous in 1986, whereas childbirth reduced or eliminated menstrual pain. There was, however, no difference in the prevalence and severity of dysmenorrhoea after an abortion or miscarriage. A possible explanation for this observed difference is to be found in histological studies concerning the influence of pregnancy on uterine neuro-transmitters and the observed reduction or disappearance of dysmenorrhoea after childbirth (Sjöberg 1979). An almost complete disappearance of uterine adrenergic nerves and a decrease in uterine noradrenaline has been demonstrated in the last trimester of human pregnancy. After term pregnancy there is only a partial regeneration of these nerve terminals and noradrenaline concentrations never reach prepregnancy values. The network of adrenergic nerves and noradrenaline concentrations were, however, unchanged in patients where the pregnancy had terminated in miscarriage or abortion. Thus altered neuromuscular activity in the uterus, due to neuronal degeneration following term pregnancy, may explain the disappearance or reduction of menstrual pain after childbirth

Our results from 1981 and from the present study have clearly demonstrated that dysmenorrhoea was significantly less frequent in users of oral contraceptives. This beneficial effect of oral contraception has been reported previously (Ylikorkala & Dawood 1978; Milsom & Andersch 1984*a;* Lumsden 1985).

In the present study the prevalence and severity of dysmenorrhoea was increased in smokers compared with non-smokers, and the severity increased significantly with the number of cigarettes smoked per day. These findings are in agreement with the recent report by Pullon *et al.* (1988) who also reported a positive correlation to cigarette smoking. Åkerlund *et al.* (1975) demonstrated reduced endometrial blood flow in women with dysmenorrhoea using a thermistor probe technique. Cigarette smoking is known to cause vasoconstriction, but we are unaware of any studies investigating the effect of cigarette smoking on uterine blood flow in the non-pregnant uterus. Thus, the exact mechanisms behind this observation remain unclear. It is also possible that there are psychological differences between smokers and non-smokers regarding the subjective experience of pain

This study has demonstrated that factors such as parity, the use of oral contraception, smoking habits, menstrual pattern and menarcheal age influence the prevalence and severity of dysmenorrhoea, whereas increasing age alone seems to have little influence.

Medical requirements and absenteeism were significantly reduced in 1986 compared with 1981. In particular the number of women absent every or alternate menstruations was much lower in 1986 than was reported in 1981. However, it was apparent from the present study that the daily activity of a large number of 24-year-old women was still affected by the occurrence of dysmenorrhoea. Only 55% of the women with dysmenorrhoea consumed analgesics or were taking the oral contraceptive pill because of dysmenorrhoea. It is somewhat surprising to note that a large number of women with dysmenorrhoea still apparently suffer in silence, despite the availability of effective treatment (Milsom & Andersch 1984b).

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Cyclic changes in composition and volume of the breast during the menstrual cycle, measured by magnetic resonance imaging

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Summary. The volumes and spin-lattice (T_1) relaxation times of breast tissues and parenchymal water content were measured non-invasively by magnetic resonance imaging (MRI) in eight healthy women during four to eight consecutive menstrual cycles. Total breast volume, and parenchymal volume, T_1 relaxation time and water content were lowest between days 6 and 15. Between days 16 and 28, parenchymal volume, T_1 relaxation time and water content rose sharply by 38·9%, 15·1% and 24·5%, respectively, and peaked after day 25. Within 5 days of the onset of menses, parenchymal volume fell sharply by 30·3%, while water content declined by 17·5%. Rising parenchymal volume in the second half of the menstrual cycle is not solely due to increased tissue water content and provides in vivo evidence for both growth and increased tissue fluid at this time.

Changes in size, histology and activity of the breast during the menstrual cycle in adult women have attracted considerable clinical attention (McCance *et al.* 1937; Ferguson & Anderson 1981*a, b*; Vogel *et al.* 1981; Anderson *et al.* 1982; Going *et al.* 1988). Techniques for volume estimation, including water displacement (Hytten 1954; Milligan *et al.* 1975) and plaster casting (Ingleby 1949), provide no information about changes within the breast, while techniques such as mammography and ultrasound do not readily provide volumetric data Detailed studies of composition or activity require invasive techniques such as the excision of healthy tissue during surgery (Potten *et al.* 1988). Magnetic resonance imaging (MRI) has been used to characterize breast tissues, including studies of spin-lattice (T_1) relaxation during the menstrual cycle (Nelson *et al.* 1985; Martin & Yousef 1986). The T_1 relaxation time is a measure of the rate of energy loss from tissues following NMR excitation. This energy loss is dependent upon the biophysical environment of the excited protons. A short T_1, therefore, indicates the presence of lipids and/or organic structures which can bind cellular water tightly A longer T_1 is expected from tissues of greater hydration and with the greatest amount of cellular water. Volumetric studies of the breast have been made using MRI (Foster & Knight 1983), and the technique can also be employed

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to estimate non-invasively the water content of non-fatty tissues (MacLennan *et al.* 1986).

The aim of the present pilot study was to investigate MRI-detectable patterns of change, including alteration in parenchymal water content, within the breast during the menstrual cycle. Differences due to parity and the use of oral contraceptives were also examined.

Subjects and methods

Eight healthy women, mean age 34·4 (SD 7·6) years, took part in the study. The average bodyweight was 56·7 (SD 8·2) kg, mean height was 1·62 (SD 0·03) m, and the average BMI (body-mass index = kg/m^2) was 21·7 (SD 2·6). Four women were nulliparous; three of the four parous women had breast-fed their children for 3–9 months, but not in the 12-month period preceding the study. Two nulliparous and two parous women were taking oral contraceptives. These contraceptives were: (a) Logynon (Schering) which gives a progesterone (levonorgestrel: 50–125 μg/day) dose rising during the cycle and highest oestrogen just after mid-cycle (ethinyloestradiol: 40 μg/day on days 14–18, otherwise 30 μg/day), and (b) Norinyl-1 (Syntex) which gives constant oestrogen/progesterone doses (mestranol 50 μg/day, norethisterone 1 mg/day). In both cases no dosage is taken on days 1–7 of the menstrual cycle. The study was approved by the Grampian Health Board Joint Ethical Committee and informed consent was obtained from all subjects.

Water displacement. In three women breast volumes were measured by water displacement on three, six and six occasions, using a technique based on that described by Milligan *et al.* (1975). These measurements were made within 4 h of MRI measurements.

MRI methods

The subjects were imaged using the Aberdeen 3·4 MHz (0·08 Tesla) NMR proton imager. Three imaging pulse sequences were used for the following three separate types of measurement.

Volume measurements. Volumes of both breasts combined were calculated from serial images using an inversion recovery (IR) pulse sequence (repetition time, Tr = 370 ms, interval, Ti = 170 ms). This pulse sequence gives a contrast of 1:2·8 between muscle and fat signal intensities (Fowler *et al.* 1988) and image collection time is 47s. Serial IR images were collected through the chests of supine subjects, from anterior to posterior limits of the breasts, at 2-cm intervals The relaxation time of parenchyma was determined in a subject before the start of the study. Bottles ranging between 164 and 1190 ml in volume, and containing $CuSO_4$ solutions, of similar T_1 relaxation to parenchyma, were used to estimate the error in MRI calculation of volumes. The bottles were imaged at 2-cm intervals.

Estimation of water content. A single saturation recovery (SR) image (Tr = 1500 ms) was collected through the middle of the breasts of each woman during each imaging session. The women had an 80:20 water/deuterium test object on their chests during image collection. The Tr of this pulse sequence was five times longer than parenchymal T_1 relaxation time, enabling the collection of images which had signal intensities proportional to the water content of non-fatty tissues (MacLennan *et al.* 1986). Since deuterium does not contribute to the NMR signal at proton frequencies, it can be used to dilute water to obtain tissue-equivalent concentrations. Water/deuterium test objects, with water/deuterium ratios of 60:40, 70:30, 80:20, 90:10 and 100:0, were imaged at the start of each imaging session, providing a standard curve for NMR signal intensity of the SR images against water content. All SR image signal intensity values were expressed as a ratio of the 80:20 water/deuterium test object signal intensities to compensate for day-to-day variation in imager performance. In order to obtain a correction factor between MRI estimated and actual water contents of lean tissues, 5 kg of lean muscle, wrapped around an 80:20 water/deuterium test object, was imaged 15 times using the SR pulse sequence. Subsequently 35 strips of 5 g each were cut from the muscle and dried to constant weight at 60°C, the difference between initial and final weights providing the water content of the muscle. The water content of muscle is around 70–80%, compared to parenchymal water content of 70·6 (SD 20·6)% (Soman *et al.* 1970). Since emphasis in the present study is placed on the way in which water content changes, rather than specific values for water content, any errors in estimating water content are therefore compensated for when subjects and stages of the menstrual cycle are compared.

T_1 relaxation time measurement. A T_1 relaxation time map of the breast was calculated from an interleaved SR/IR image (Tr = 1000 ms, Ti = 200 ms collected through the middle of the breasts of each woman on each occasion. T_1 relaxation time values for fat and parenchyma were then measured from specified regions of interest.

Image analysis. The images were analysed with a mini-computer and in-house raster graphics emulating display system. On the IR images (Fig. 1a) fatty tissues were white while lean tissues were dark. Automatic and interactive image analysis techniques were combined to obtain quantitative information, including area (cm^2), image intensity or T_1 relaxation time, from regions of interest. The term 'parenchyma' was used for all non-fatty tissues of the breast, including lobular and non-fatty stroma. On each SR image (Fig. 1b) two areas (2 cm^2) of parenchymal tissue in each breast were outlined and SR image intensity recorded. From each map (Fig. 1c) two areas of fatty and parenchymal tissues (each 2 cm^2) were used to determine the in-vivo relaxation times of fat and parenchyma. Using a simple truncated cone model (Kvist *et al.* 1987), volumes were extrapolated from the measured areas of test objects or tissues in consecutive IR images. The error of volume calculation from MRI images was determined by subtracting MRI-calculated from the known volumes of the test objects, and expressing the product as a percentage of the known volumes. The repeatability of the methods used was determined by analysing the same set of images four times, calculating volumes and expressing the result as a percentage deviation from the mean volume.

Statistical analysis

The menstrual cycle was divided into three periods of roughly equal number of days (days 1–10, 11–20, 21–28: day 1 = onset of menses) and differences due to subjects and days in the raw data were analysed by two-way analysis of variance (two-way ANOVA). The number of day-groups was limited to three to maximize the number of replicates in each group. To examine

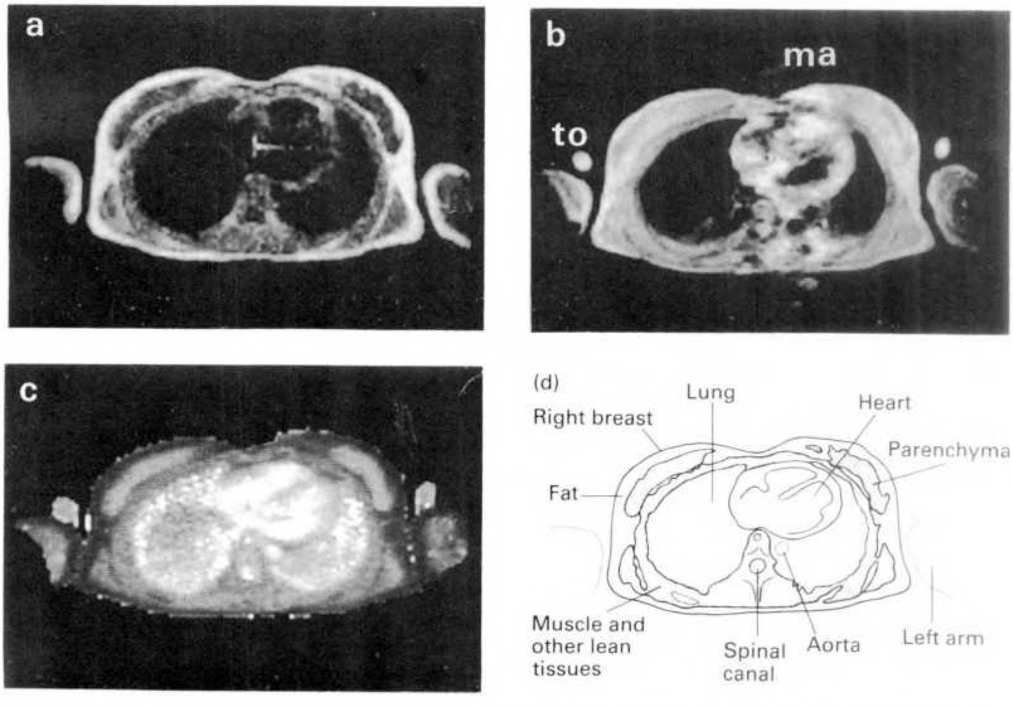

Fig. 1. Examples of the three MRI image types used: (a) IR image for volume calculation, (b) SR image for parenchymal water content estimation, (c) T_1 image for measurement of fatty tissue and parenchymal T_1 relaxation times; (d) drawing showing main features visible in the images. to, Test object; ma, motion artifact; blurring of heart and surrounding tissues due to heart beat.

changes during the menstrual cycle in more detail the menstrual cycle was divided into 6-day periods (days 1–5, 6–10, 11–15, 16–20, 21–25, day 26 onwards). Differences between the number of measurements during each day-group in each woman were compensated for by taking the mean of each variable, during each day-group, for each woman. Therefore each subject contributed only one data point for each variable in each day-group. To compensate for the considerable inter-cycle variation and differences between individuals, measurements were expressed as a percentage of the values measured during menses for each subject. Inter-cycle variability was calculated from images collected on the same day during successive menstrual cycles in each subject. The volumes in the first cycle were expressed as a percentage of volumes in the second cycle. Differences between volumes, water content, or T_1 relaxation during different day-groups were tested by paired *t*-test. The effects of parity or use of oral contraceptives were tested by two-way analysis of variance (two-way ANOVA). Relations between variables were tested by least-squares linear regression and correlation coefficient *(r)*. MRI and water displacement techniques for estimating total breast volume were compared using the method of Bland & Altman (1986).

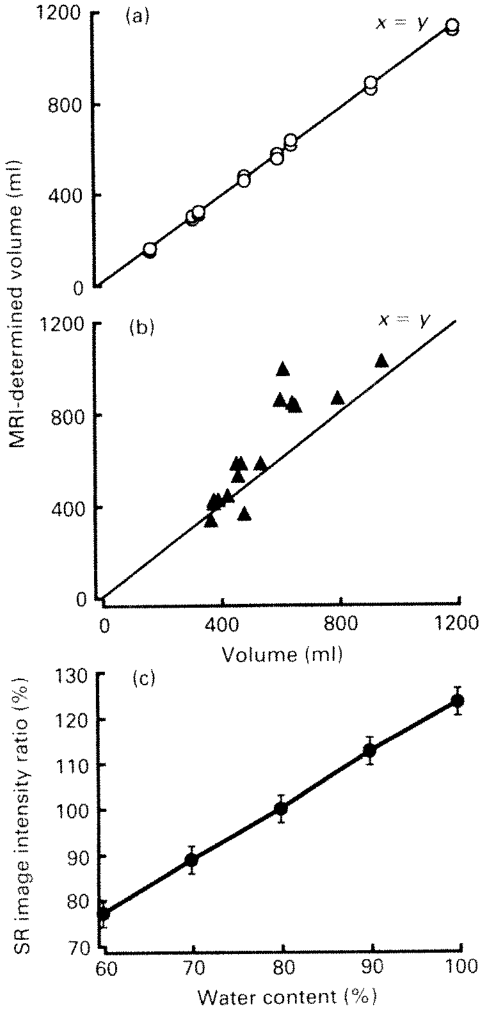

Fig. 2. Determination of imager performance: (a) the relation between MRI-determined and known volumes of test objects, (b) the relation between total breast volumes determined by MRI and by water displacement, (c) the relation between SR image signal intensity, expressed as ratios relative to the SR image signal intensity of an 80:20 water/deuterium test object, and water content of water standard test objects.

Results

Between nine and 18 measurements (mean 12, SD 3) were obtained from each woman during 4–8 consecutive menstrual cycles (mean 5, SD 1) with an average of three measurements made during each cycle. The individual imaging time for each subject ranged between 20 and 30 min.

Calibration of MRI measurements

The error of volume calculation from IR images was −5·7 (SD 1·3)%, indicating slight underestimation of volume calculation (Fig. 2a), while repeatability, expressed as a percentage of mean volume, was 4·3 (SD 2·7)%. Mean breast volumes as calculated by MRI (641·3, SD 239·8 ml) were significantly higher (paired *t*-test $t = 2·93$, $P<0·05$) than those measured by water-displacement (544·6, SD 163·4 ml). In the case of smaller breasts water displacement produced estimates of breast volume 3% larger than MRI, but 20%

Table 1. Breast characteristics in eight women

Variable		Mean	(SD)
Total breast volume	(ml)	890·0	(578·9)
Parenchymal volume	(ml)	281·7	(119·5)
Fatty tissue volume	(ml)	601·4	(483·2)
Fatty tissue T_1	(ms)	161·6	(9·9)
Parenchymal T_1	(ms)	326·3	(50·9)
Parenchymal water	(%)	75·6	(13·2)

Table 2. Values for changes in parenchymal tissue during the menstrual cycle

Days	Parenchymal volume (ml)	Parenchymal T_1 (ms)	Parenchymal water (%)	*n*
1–10	266·1 (6·2)	328·0 (5·1)	72·2 (1·8)	32
11–20	255·7 (6·9)	312·0 (5·7)	70·4 (2·0)	29
21–28	322·1 (6·6)	337·0 (5·4)	83·9 (1·9)	32

Values are derived from two-way ANOVA and are expressed as mean (SE) with SE adjusted by two-way ANOVA to exclude variability due to inter-subject variability, concentrating on the effect of stage of menstrual cycle.
n, Number of observations.

smaller than MRI in the case of large breasts (Fig. 2b), suggesting that results from these two techniques are not clinically comparable.

The relation between SR image intensity and the water content standards was linear ($y = 0{\cdot}0677 + 0{\cdot}0116x$, $r = 0{\cdot}998$, $P<0{\cdot}001$) and is shown in Fig. 2c. The water content of the lean muscle determined by drying to constant weight was 73·2 (SD 1·2)%. The ratio between the SR image signal intensities of muscle and the 80:20 water/deuterium test object was 0·72 (SD 0·01), which converts to 56·2 (SD 1·3)% water using the standard curve relating SR image intensity ratios to water content. Therefore estimates of parenchymal water content were multiplied by a correction factor of 1·3 and expressed as a percentage.

Changes in the breast during the menstrual cycle

Table 1 gives inter-individual variation in all variables measured. Inter-cycle variation of breast volumes within individuals was slight (5·7, SD 12·0%) and not significant (paired *t*-test $t = 1{\cdot}25$, $P>0{\cdot}05$). Two-way analysis of the raw data showed that there was significant variation in all characteristics between subjects ($F = 4{\cdot}17$–$773{\cdot}36$, $P<0{\cdot}01$–$0{\cdot}001$). Comparing changes between days 1–10, 11–20 and 21–28 (two-way ANOVA, Table 2), there were significant differences in total volume ($F = 5{\cdot}03$, $P<0{\cdot}05$), parenchymal volume ($F = 28{\cdot}75$, $P<0{\cdot}001$), parenchymal T_1 ($F = 4{\cdot}32$, $P<0{\cdot}05$) and parenchymal water content ($F = 11{\cdot}94$, $P<0{\cdot}001$), but not fat volume ($F = 0{\cdot}22$, $P>0{\cdot}05$) or fat T_1 ($F = 0{\cdot}82$, $P>0{\cdot}05$). Parenchymal volume (Fig. 3) and T_1 relaxation time (Fig. 4) rose during the second half of the menstrual cycle (Table 3) and reached their highest values just before menses. In less than 5 days after the onset of menses, parenchymal volume fell by 30·3% (paired *t*-test, $t = 4{\cdot}56$ $P<0{\cdot}001$), while the fall in parenchymal T_1 relaxation time was only 7·7% (paired *t*-test, $t = 2{\cdot}75$ $P<0{\cdot}05$).

Both fat and parenchymal T_1 times were correlated with the proportion of fatty and lean tissue in the breast ($r = 0{\cdot}528$–$0{\cdot}546$, $P<0{\cdot}01$): the higher the breast fat content the lower the parenchymal T_1 relaxation times. This may be due to the intermixing of fat and parenchymal tissues which were less clearly differentiated in the fatter breasts. Although estimated parenchymal water content rose significantly during the second half of the menstrual cycle (Table 3), this increase is unlikely to account for more than 65% of the large rise in parenchymal volume since, even if parenchyma was 100% water, a 24·5% increase in the amount of water would not produce a 38·9% increase in volume. However, estimated parenchymal water content fell by 17·5% between days 26+ and days 1–5 (paired *t*-test, $t = 3{\cdot}49$, $P<0{\cdot}01$). Furthermore, parenchymal water content was lowest between days 6 and 10 while parenchymal volume continued to decline until days 11–15.

Differences associated with parity and oral contraceptives

Two-way ANOVA was repeated with subdivisions of parous/nulliparous and oral contraceptive/no oral contraceptive. There was a tendency for smaller changes in parenchymal volumes (25·7% *vs* 32·3%, $F = 13{\cdot}18$, $P<0{\cdot}001$) in parous subjects who also tended to show larger changes in parenchymal water content (29·4% *vs* 16·3%, $F = 2{\cdot}28$, $P>0{\cdot}05$). Subjects using oral contraceptives tended to have smaller changes of parenchymal volumes (24·5% *vs* 31·8%, $F = 5{\cdot}43$, $P<0{\cdot}05$) and parenchymal water content (18·0% *vs* 20·2%, $F = 0{\cdot}21$, $P>0{\cdot}05$) than those not using oral contraceptives. Subjects using Logynon showed a correlation between highest parenchymal volume and highest progesterone doses ($r = 0{\cdot}501$–$0{\cdot}762$, $P<0{\cdot}05$). There was no significant correlation ($r = 0{\cdot}019$, $P>0{\cdot}05$) between either the oestradiol or progesterone doses and breast characteristics in subjects using Norinyl-1.

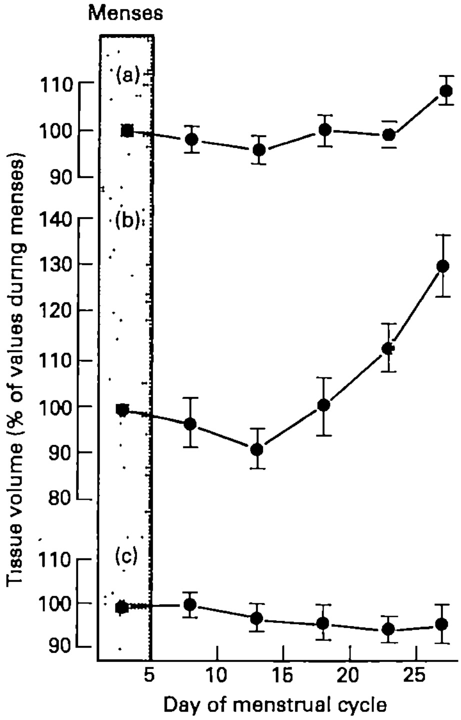

Fig. 3. Changes in the volumes of (a) total breast, (b) parenchyma, (c) fatty tissues during the menstrual cycle Values are mean ± SE for eight women and are expressed as a percentage of values measured during menses. The shading shows the duration of menses

Discussion

The present study has demonstrated changes within the breast during the menstrual cycle *in vivo*, showing that there are marked increases in total breast and parenchymal volumes, and parenchymal T_1 relaxation time and water content between middle and latter parts of the menstrual cycle In common with previous studies of the human breast (Ingleby 1949), we found marked individual variability in breast volume. The use of two-way ANOVA and the expression of data as percentages of values measured during menses in each individual permitted analysis of trend throughout the cycle in spite of high inter-subject variability.

Fowler *et al.* (1990) demonstrated that MRI could be used to measure accurately volumes of both test objects and mammary glands in the goat. The attainment of similar levels of accuracy of test object volume measurement in the present study is encouraging, although direct validation of human MRI measurements by dissection was obviously not possible. The linear relation between SR image signal intensity ratios and water/deuterium ratios of test objects suggests that measured changes in water content during the menstrual cycles were valid. The range of parenchymal T_1 relaxation times correlated with the amount of parenchyma in the breast ($r = 0{\cdot}638$; $P<0{\cdot}01$); the smaller the proportion of parenchyma, the greater the heterogeneity of the parenchymal tissues and the lower the T_1 relaxation time.

Increases in total breast volume between mid and late cycle observed in the present study are similar to, but less variable than, the 8–44% range of changes measured by conventional techniques (McCance *et al.* 1937; Ingleby 1949; Milligan *et al.* 1975). Using MRI, Nelson *et al.* (1985) and Martin & Yousef (1986) found mid to late cycle rises in T_1 relaxation times, and both studies also showed considerable variability between individuals. The present study showed

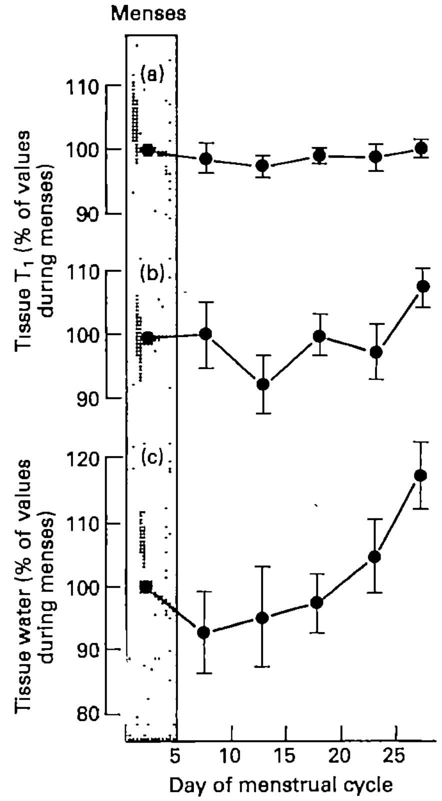

Fig. 4. Cycle-normalized changes in (a) fatty and (b) parenchymal T_1 relaxation times; (c) parenchymal water content during the menstrual cycle Values are mean ± SE for eight women and are expressed as a percentage of values measured during menses The shading shows the duration of menses

Table 3. Timing and extent of maxium changes in breast tissues during the menstrual cycle in all subjects

	Timing of change (days of cycle)		Extent of change (%)*	Paired *t*-test	
	Minimum	Maximum		*P*	*t*
Total breast volume	10–15	26+	12 8	<0·01	3·37
Parenchymal volume	10–15	26+	38·9	<0·001	8·10
Parenchymal T_1	10–15	26+	15·1	<0·001	6·39
Parenchymal water	6–10	26+	24·5	<0·001	4·70
Fatty tissue volume	21–25	1–5	5·4	NS	1·99
Fatty tissue T_1	10–15	1–5	3·0	NS	1·49

* Expressed relative to values measured during menses

that significant increases in parenchymal T_1 occur during the second half of the cycle. Significant increases in parenchymal water content between mid and late cycle have not been reported previously, but are unlikely to account for more than 65% of the 38·9% increase in parenchymal volume. Preece *et al.* (1975) reported that total body water was not correlated with any symptom of mastalgia in 56 women. However, the present study indicates that there is a localized rise in parenchymal water content during the latter half of the menstrual cycle which could contribute to symptoms of mastalgia.

Most studies of internal changes in the breast during the menstrual cycle have, to date, been in-vitro studies of excised tissue. Vogel *et al.* (1981) found distinct cycle-related histological changes in tissues from the breasts of 173 women who underwent mammoplasty or mastectomy for reasons other than neoplasia. Ferguson & Anderson (1981*a,b*) found that mitotic and apoptotic indexes peaked around days 25 and 28 respectively. Vogel *et al.* (1981) showed that by days 3–7 there was barely any active secretion, the acinar-ductular lumen were tight and mantle tissues were dense. This is reflected in the present study by declining parenchymal volume and water content. Vacuolization and enlargement of lumen after day 15 (Vogel *et al.* 1981) coincided with parenchymal volume and water content rising, and the secondary peak in parenchymal T_1 relaxation between days 16 and 20, seen in the present study. The sharp rise in parenchymal volume during the latter half of the menstrual cycle may result from increased cell size or numbers at this time, since others have found a peak in mitotic activity of lobular cells around day 25 (Masters *et al.* 1977; Ferguson & Anderson 1981*a,b*). Similarly, the sharp fall in parenchymal volume after the onset of menses may reflect the peak in apoptosis at day 28 reported by Ferguson & Anderson (1981*a,b*).

The effects of parity and use of oral contraceptives, although from a very small sample in the present pilot study, deserve comment. Reduced changes in volume, T_1 and water content of parenchymal tissues during the oral contraceptive cycle agree with previous comparisons of changes in breast volumes (Milligan *et al.* 1975). During pregnancy there is a marked increase in lobule formation, the lobules becoming large and numerous (Neville & Daniel 1980), while post-lactational changes involve the collapse of acinar structures and narrowing of lobules. The high proportion of dendritized glandular tissue in the breast, and the high apoptotic indices (Potten *et al.* 1988), in parous women probably account for the tendency towards smaller volumetric changes and larger parenchymal water content changes seen in parous women during the present study. The correlation between changes in parenchymal volume and progesterone doses in subjects using a phased-dose oral contraceptive agrees with the suggestion by Potten *et al.* (1988) that progesterone is mitogenic in women *in vivo*. More information on the lag between alterations in plasma hormone levels and changes in breast tissues is required in view of suggestions that progesterone may be anti-oestrogenic in certain circumstances (Mauvais-Jarvis *et al.* 1986).

The present study has demonstrated that MRI can be used to provide in-vivo information of gross and some internal changes in the human breast and may be suitable for further studies of the breast during the menstrual cycle, gestation and lactation.

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Doppler echocardiographic assessment of time to peak velocity in the aorta and pulmonary artery of small for gestational age fetuses

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Summary. The time to peak velocity was measured at the level of the ascending aorta and pulmonary artery by Doppler echocardiography in 38 small-for-gestational age (SGA) fetuses before and during maternal hyperoxygenation. The values were compared to a reference range derived from the study of 142 appropriate-for-gestational age (AGA) fetuses. In the SGA fetuses the time to peak velocity at the level of pulmonary artery was significantly lower and at the level of the aorta significantly higher than in AGA fetuses. During maternal hyperoxygenation the aortic time to peak velocity decreased towards normal range but there was no significant change at the level of the pulmonary artery. These results may indicate variations of aortic and pulmonary pressures in SGA fetuses that can be partially modified by maternal hyperoxygenation and which may be associated with changes in the peripheral resistance of the cerebral circulation.

Doppler echocardiography by providing a non-invasive assessment of blood flow has recently allowed the study of intracardiac haemodynamics in the human fetus.

Cross-sectional and longitudinal studies of healthy fetuses have provided reference ranges of blood flow velocities at the level of either atrioventricular valves and great arteries (Reed *et al.* 1986, De Smedt *et al.* 1987, Allan *et al.* 1987). However, there is a scarcity of reports on intracardiac haemodynamic changes in fetuses with abnormal peripheral vascular resistance such as those with intrauterine growth retardation, and the results so far obtained are contradictory (Reed *et al.* 1987, Rizzo *et al.* 1988, Al-Ghazali *et al.* 1989).

Previous Doppler studies have demonstrated that in chronically hypoxic small-for-gestational age (SGA) fetuses the impedance to blood flow in the descending aorta is increased (Jouppila and Kirkinen 1984) with a concomitant decrease in cerebral vascular resistances (Wladimiroff 1986). This phenomenon, the so called brain sparing effect that is well described in experimental models on animals exposed to acute or

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chronic hypoxia (Peeters *et al.* 1979), seems to be reversed by maternal hyperoxygenation (Nicolaides *et al.* 1987, Arduini *et al.* 1988).

An inverse relation between Doppler-measured time to peak velocity (TPV) and the mean arterial pressure has been established both in newborns and in adults with pulmonary hypertension (Kitabatake *et al.* 1983, Kosturakis *et al.* 1984). Furthermore on the basis of TPV studies (Machado *et al.* 1987), it has been suggested that in healthy fetuses the mean pressure in the pulmonary artery is higher than in the ascending aorta, reflecting a difference in resistance between the two circulations. There is no account, however, as to whether the fetal brain sparing condition affects the blood pressure at the level of the ascending aorta and the pulmonary artery and on the eventual relations between these changes with peripheral vascular resistance. The aim of the present investigation was to establish whether Doppler-detectable variations in TPV are present in SGA fetuses at the level of the aorta and pulmonary artery and to examine whether these variables can be modified by maternal hyperoxygenation.

Subjects and methods

Reference ranges of TPV in aorta and pulmonary artery were constructed from the cross-sectional study of 142 appropriate-for-gestational age (AGA) fetuses. This group of 142 fetuses was selected from a population of 154 low risk pregnancies recruited from our antenatal clinic; 12 women were excluded because they subsequently developed pregnancy complications. All pregnancies were singleton and accurately dated by certain last menstrual period and early second trimester ultrasonography. Ultrasound scans at the time of Doppler studies showed all the fetuses to be structurally normal and of appropriate size for gestational age. Infants were born in good conditions at a mean gestational age of 39·8 weeks (SD 2·1; range 38–43) and birthweights were appropriate for gestational age (3420 g, SD 412, range 2700–4350).

TPV were also measured in 38 SGA fetuses. The SGA fetuses studied fulfilled all the following criteria: (i) singleton pregnancy accurately dated; (ii) abdominal circumference < 5th centile (Campbell and Wilkin 1975); (iii) absence of congenital abnormalities (i.e. malformations, genetic diseases); (iv) Doppler flow velocity waveforms (FVW) in umbilical artery, descending thoracic aorta and internal carotid artery abnormal (pulsatility index <2 SD and >2 SD) for our reference ranges (Arduini *et al.* 1987); (v) fetal vascular response to maternal hyperoxygenation demonstrated by a temporary recovery towards normal values of FVW at the level of internal carotid artery and descending aorta (Arduini *et al.* 1989) after 20 min of treatment. The characteristics of the SGA fetuses are given in Table 1. The mean gestational age at the time of the recordings was 30·4 weeks (SD 4·9; range 20–38) in AGA and 30·8 (SD 3·0; range 24–36) in SGA fetuses.

All the patients gave their informed consent to participation in the study.

A commercially available Ansaldo Esacord 81 colour Doppler equipment with 3·5 or 5 MHz convex probes was used for all measurements. In addition to the colour flow mapping function the machine is equipped with a pulsed Doppler with a carrier frequency ranging from 2·5 to 5 MHz. Recordings were performed with the woman lying in a comfortable semirecumbent position during phases of fetal rest without breathing movements. The fetal heart was first examined using two-dimensional echocardiography to exclude congenital cardiac abnormalities. The pulmonary artery and the ascending aorta were then imaged respectively in short axis and five chamber views. The colour flow mapping function was then superimposed and the aortic and pulmonary flows demonstrated. Care was taken to image the flow so that it was parallel to the Doppler beam. The flow was sampled immediately distal to valve leaflets and velocity waveforms were recorded. Recordings at a beam angle larger than 30° were rejected.

Oxygen was administered to the woman for 20 min through a face mask delivering about 60%

Table 1. Characteristics of the small for gestational age fetuses studied

Gestational age at delivery (weeks) mean (SD)	34·3	(4·2)
Emergency caesarean section for fetal distress % (*n*)	63·1%	(24)
Birthweight (g) mean (SD)	1824	(326)
Birthweight		
<5th centile % (*n*)	79%	(30)
5th–10th centile % (*n*)	21%	(8)
Pulsatility index (PI) mean(SD)		
Umbilical artery	1·94	(0·38)
Descending aorta	2·92	(0·36)
Internal carotid artery	1·14	(0·23)

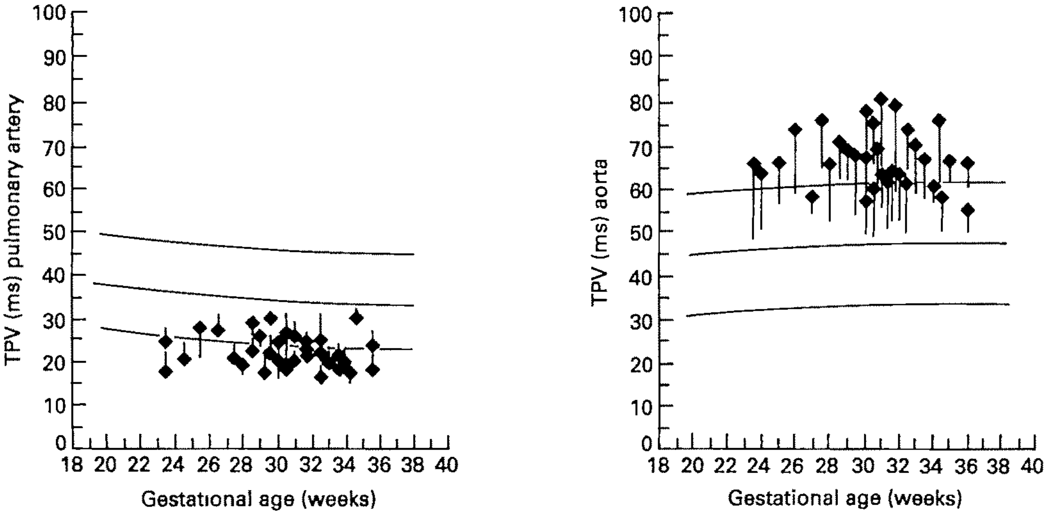

Fig. 1. Time to peak velocity (TPV) from pulmonary artery and aorta before (points) and 20 minute after (vertical lines) maternal administration of 60% oxygen in small-for-gestational age fetuses. Normal ranges for gestation are shown as mean ± 2 SD

humidified oxygen. Recordings were performed before (basal value) and after 20 min of oxygen administration with the woman still breathing oxygen. Permanent FVW records were obtained with a strip chart recorder. The print-outs were labelled with random numbers for subsequent analysis. Observers involved in the later analysis were not informed of the sequence of the print-outs.

Pulmonary and aortic time to peak velocities were calculated as the time-differences from the onset of the waveform to its peak velocity. Ten consecutive velocity waveforms were selected and the values obtained averaged. Measurements were obtained using a high resolution digitizing tablet interfaced to a computer (Cardio 800, Kontron). Fetal heart rate was estimated from the Doppler tracings.

To assess reproducibility 10 AGA fetuses and five SGA fetuses were studied 'blind' by two observers for two consecutive days. The intra-observer and inter-observer variation did not exceed respectively 8% and 10% for the TPV measurements performed at the level of both aorta and pulmonary artery.

Statistical analysis was performed on a Macintosh II computer using the Stat View II statistical package (Abacus Concepts Inc., Berkeley, California, USA).

Regression analysis was used to establish the reference limits of TPV with gestation. Differences were analysed using the unpaired and paired *t*-tests.

Results

Reliable recordings of TPV from both aorta and pulmonary artery were obtained in 121 AGA (85%) and in 30 SGA fetuses (79%), in 15 AGA (11%) and in six SGA fetuses (16%) recordings were measured only from pulmonary artery whereas in the remaining six AGA (4%) and two SGA fetuses (5%) only the aortic TPV was obtained.

In AGA fetuses no significant changes with gestational age were found in TPV of pulmonary

Table 2. Comparison between time to peak velocity (TPV) values between appropriate-for-gestational age (AGA) and small-for-gestational age (SGA) fetuses.

	AGA fetuses		SGA fetuses	
	n	Mean (SD)	*n*	Mean (SD)
TPV aorta (ms)	131	46.4 (6·9)	32	65·2 (8.1)*
TPV pulmonary artery (ms)	136	34·2 (6·4)	36	23·4 (7·5)*

Significance of difference between the AGA and SGA fetuses **P*<0·001 (unpaired *t* test).

Table 3. Time to peak velocity (TPV) and fetal heart rate (FHR) values before (basal) and 20 min after maternal hyperoxygenation in the small-for-gestational-age fetuses

	n	Basal values	20 min after oxygen	Mean (SD) difference
TPV aorta (ms)	32	65·2 (8·1)	53·4 (9·3)	9·2 (3·4)*
TPV pulmonary artery (ms)	36	23·4 (7·5)	23·8 (7·6)	0·54 (1·4)
FHR (beats/min)				
Aorta	32	134·2 (12·7)	136 (14·3)	1·84 (2·3)
Pulmonary artery	36	137·1 (9·9)	135·2 (8·6)	2·01 (1·8)

Results are mean (SD) values Significance of difference between before and after treatment.
*$P < 0·001$ (paired t-test).

artery ($r = 0·18$, constant = 0·43, slope = 0·003) and in aortic TPV ($r = 0·12$, constant = 0·43, slope = 0·001).

In SGA fetuses the TPV at the level of the aorta was significantly higher and in pulmonary artery significantly lower than in AGA fetuses (Table 2). During maternal hyperoxygenation there was a significant decrease in TPV at the level of aorta with a recovery towards normal values but no significant change was observed in the pulmonary artery (Fig. 1). The changes observed in TPV 20 min after the beginning of oxygen administration are given in Table 3. No significant modifications of fetal heart rate was found during oxygen administration (Table 3).

Discussion

In intrauterine life the output of the left ventricle is directed through the ascending aorta to the upper body organs, including the brain and the heart, whereas the output of the right ventricle is directed to the pulmonary circulation and throughout the patent ductus arteriosus to the lower body and placenta.

Machado *et al.* (1987) first noted that in healthy fetuses TPV was shorter in the pulmonary artery than in the aorta, suggesting higher arterial mean pressure in the pulmonary circulation. Furthermore no significant changes of either TPV were reported during gestation (Virginia *et al.* 1989) whereas TPV in the pulmonary artery lengthened in the neonatal period (Wilson *et al.* 1987).

Our findings of a significant increase in aortic TPV in the SGA fetuses suggest a decrease in mean arterial pressure at the level of the ascending aorta which is presumably secondary to decreased cerebral vascular resistance. The concurrent shortening of TPV in the pulmonary artery of these fetuses is probably a consequence of increased pulmonary and peripheral vascular resistance.

Maternal hyperoxygenation increases fetal $P\mathrm{O}_2$ levels (Nicolaides *et al.* 1987) and in SGA fetuses is associated with modifications towards normal values of FVW recordings from cerebral vessels and descending aorta (Arduini *et al.* 1988). An increase in fetal cerebral vascular resistance may explain the decrease of aortic TPV found during maternal oxygen administration. On the other hand the significance of the lack of changes in the pulmonary TPV is more obscure. Possibly the increased fetal $P\mathrm{O}_2$ levels may cause a relative constriction of the ductus arteriosus (McMurphy *et al.* 1972) so minimizing the effects of the decreased vascular resistance of the fetal lower body. On the other hand, a chronic increase of peripheral vascular resistances, as found in SGA fetuses, may be responsible for morphological alterations in pulmonary vessels (Levin *et al.* 1978) causing a permanent increase in pulmonary vascular resistance. This is supported by the results recently reported by Siassi *et al.* (1988) who studied a group of newborn associated with intrauterine growth retardation and found pulmonary hypertension despite the absence of cardiopulmonary compromise.

In conclusion, in SGA fetuses there is a decrease of aortic TPV and this is reversed by maternal hyperoxygenation whereas the TPV in the pulmonary artery is shortened but remains unaffected by maternal oxygen administration. Further longitudinal studies during the perinatal period are therefore required to better clarify the significance of these haemodynamic changes and their sequelae during the neonatal period and such studies are in progress.

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The influence of suture material on vaginal vault granulations following abdominal hysterectomy

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Summary. A questionnaire was circulated to 1147 members (consultant status) and fellows of the Royal College of Obstetricians and Gynaecologists to survey the current management of the vaginal vault following abdominal hysterectomy. Of the 56% who responded, the majority (87%) routinely close the vault. An interrupted mattress suture is used by 60%, a continuous suture by 43% and the Lembert suture by 2%. Chromic catgut is favoured by 60%, a synthetic polymer by 33% and plain catgut by 6%. We then organized a prospective, randomized trial involving 114 women who underwent total abdominal hysterectomy for benign indications. No. 1 polygalactide (Vicryl) was used in 58 women, and No. 1 chromic catgut in 56. Overall, 37 (32%) had vault granulations 6 weeks post-operatively. Chromic catgut had been used in 25 (68%) and polygalactide in the remaining 12 (32%) ($P = 0{\cdot}01$). Only 2 (5%) of these women denied any symptoms, while the rest complained of vaginal discharge, bleeding or both. Neither the patients' age, weight or parity, nor the status of the surgeon influenced the occurrence of granulations. We conclude that the widespread use of chromic catgut revealed by our survey is unacceptable: polygalactide, a synthetic polymer, is associated with fewer vaginal vault granulations than chromic catgut.

Vaginal vault granulations are a commonly observed sequelae of abdominal hysterectomy. Although benign, and thought to regress spontaneously over a few months, they nevertheless retard convalescence and can cause distress and disappointment after an otherwise successful operation. They may cause a copious discharge, and alarm the patient if they bleed. They also often necessitate two or three extra visits to the outpatient department for cauterization, and occasionally readmission for diathermy under anaesthesia.

It is unclear whether the occurrence of vault granulations is idiosyncratic, or is related to the suture material used or closure technique employed. Some of the manuals of operative gynaecology which address the issue (Howkins and Hudson 1983; Howkins and Stallworthy 1974) advise that the vaginal vault should be closed and advocate the use of plain catgut to minimise vault granulations. However, there is

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little information concerning actual practices among gynaecologists in the UK and Eire. Little is known about the frequency of vault granulations, or of the influence of suture material and closure technique on their occurrence. The published studies report widely disparate rates: Howkins and Williams (1968) closed the vault with chromic catgut and found granulations in 37%; while Fairlie and Al-Hassani (1973) employed the Lembert suture to close the vault and reported rates of 11% when chromic catgut was used and 3% with polyglycolic acid (Dexon).

We were curious to establish how gynaecologists in the UK and Eire currently manage the vaginal vault following abdominal hysterectomy for benign pathology. We deliberately restricted our survey population to members of consultant status and fellows of the Royal College of Obstetricians and Gynaecologists because they are more likely to have settled on a particular technique and tend to determine operative policy for their juniors.

We then followed this up by comparing the two most commonly used suture materials, chromic catgut and polygalactide (Vicryl), in a prospective randomized trial to study the influence of suture material on the occurrence of vault granulations. We also compared the two most popular closure techniques, interrupted mattress and continuous sutures.

Subjects and methods

Postal survey

A reply-paid questionnaire was circulated to 1147 members of consultant status and fellows of the Royal College of Obstetricians and Gynaecologists resident in the UK and Eire. Respondents were requested to indicate whether they routinely closed the vaginal vault following abdominal hysterectomy for benign conditions, their closure technique and choice of suture material. Their opinions were sought as to whether they regarded vault granulations to be a significant problem. They were asked to estimate the frequency of vault granulations and to indicate if they thought closure technique or suture material influenced their occurrence. Respondents were asked to state the year in which they became members of the Royal College of Obstetricians and Gynaecologists.

Comparison of polygalactide and chromic catgut

A series of 120 consecutive women undergoing elective abdominal hysterectomy for benign pathology between May 1987 and August 1988 at St Helier's Hospital were recruited to the study. On admission each woman was allocated randomly to one of two groups by the sealed opaque envelope technique.

The patients were divided into two equal groups: No. 1 polygalactide was used for vault closure in group 1 and No. 1 chromic catgut was used in group 2. Prior to sealing the envelopes and the randomization, each group had been subdivided into two equal halves: in one half a continuous suture technique was to be employed while an interrupted mattress suture was to be used in the other half.

The operations were performed by four consultants, two senior registrars and three registrars.

The women were reviewed 6 weeks after the operation and they were specifically asked if they had experienced any vaginal discharge or bleeding. A Cuscoe's speculum was used to inspect the vaginal vault. Vault granulations were recorded as present or absent. To minimise bias, the operation notes were not referred to until after the woman had been interviewed, the vaginal vault examined and the results recorded; in this way it was hoped that the observer would not remember which suture material was used if he/she had been present at the original operation.

Statistical methods

Postal survey. We requested from the College the names and addresses of all members of consultant status and fellows of the Royal College of Obstetricians and Gynaecologists who were resident in the UK and Eire; the list contained 1147 names. The data were analysed with a Dataking program on an Acorn Archimedes microcomputer. Analysis of categorical variables was by the χ^2-test.

Trial of polygalactide vs chromic catgut. We estimated that about 40% of women have vault granulations when chromic catgut is used (Howkins and Williams, 1968) and that a reduction to 15% would be clinically important. Power calculations revealed that this would require a trial involving 112 women ($\alpha = 0{\cdot}05$ (two sided); $1 - \beta = 0{\cdot}85$). We recruited 120 women to allow for the possibility of dropouts. The data were analysed with a computerized statistical package (SPSS). Analysis of categorical variables was by the χ^2 test and of continuous variables by the t-test.

Results

Postal survey

Choice of suture material. Of the 1147 questionnaires circulated, 645 were returned completed, a response rate of 56% Most of the respondents (87%) routinely closed the vault while 13% left it open. Chromic catgut was used by 60% of surgeons while 33% used a synthetic polymer and 6% used plain catgut (Table 1). Of the 216 surgeons who used a synthetic polymer, 156 (72%) preferred polygalactide, 40 (18%) used polyglycolic acid and 20 (9%) polydextrane sulphate.

Choice of closure technique. Table 1 also illustrates the choice of closure technique. Interrupted mattress was the most popular choice, and less than 3% used the Lembert suture.

Respondents' attitudes to vault granulations. Most of the respondents (70%) thought that vault granulations were a common problem. Suture material was thought to influence the occurrence of vault granulations by 45% and closure technique by 54% of respondents. Only 19% estimated the frequency of vault granulations at >20% of abdominal hysterectomies. We found that the more recently qualified surgeons tended to give the higher estimates.

Polygalactide vs chromic catgut

Comparability of study groups and exclusions. Table 2 shows that there were no significant differences between the two groups as regards age, parity and pre-operative weight. Out of the 120 women recruited into the study, six were excluded from the final analysis because the vaginal vault was subsequently left open. This was because in each case the surgeon felt that a pelvic haematoma was likely to form and that leaving the vault open would facilitate drainage. There were two exclusions from the polygalactide group and four from the chromic catgut group A total of 114 women were therefore available for analysis.

Frequency of vault granulations. Overall, 37 (32%) women had vault granulations at the 6 week post-operative review. In 25 (68%) of these women the vault had been closed with chromic catgut, whereas polygalactide was used in the remaining 12 (32%). The odds ratio of vault granulations with polygalactide compared with chromic catgut is 0·32; (95% CI 0·14 to 0·74). Of the 58 women in the polygalactide group 12 (21%) had vault granulations and of the 56 women in the chromic catgut group 25 (45%) had granulations; the difference in the occurrence of granulations between the two groups is highly significant ($P = 0{\cdot}01$). The status of the surgeon or parity of the women had no influence on the occurrence of granulations.

The influence of closure technique on the occurrence of vault granulations. An interrupted mattress suture was used to close the vault in 28 women in the polygalactide group, and of these 5 (18%) developed granulations; in the remaining 30 women a continuous suture was used and the frequency of granulations was 23%. In the chromic catgut group a mattress suture was used in 27 women, and granulations occurred in 41%, whereas a continuous suture was used in the other 29 women and 48% developed granulations. Although with both catgut and polygalactide vault granulations occurred less often when an interrupted mattress suture was used, the difference between the two techniques was not statistically significant.

Table 1. Postal survey—Choice of suture material and closure technique

Suture	Vault closed	Vault open	Total
Suture material			
Chromic catgut	342 (53%)	47 (7%)	389 (60%)
Synthetic polymer	180 (28%)	36 (5%)	216 (33%)
Plain catgut	38 (5%)	2 (0·3%)	40 (6%)
Closure technique			
Interrupted mattress	338 (52%)	12 (2%)	350 (54%)
Interlocked continuous	101 (16%)	43 (7%)	144 (22%)
Unlocked continuous	108 (17%)	29 (5%)	137 (21%)
Lembert	13 (2%)	1 (0·15%)	14 (2%)

Table 2. Age, parity and pre-operative weight of women, and grade of surgeon in the two study groups

	Polygalactide ($n = 58$)	Chromic catgut ($n = 56$)
Age (years)	42·1 (6·8)	42·5 (8·5)
Parity	2·4 (1·4)	2·4 (1·1)
Weight (kg)	59·6 (7·0)	59·1 (7·5)
Surgeon		
Consultant	21	24
Senior registrar	20	19
Registrar	17	13

Results are mean (SD) or number of operators as appropriate.

The influence of age and weight. The mean age of women with vault granulations was 41·8 years (SD 6·2), whereas that of those without was 42·9 years (SD 6·7). The mean pre-operative weight was 60·4kg (SD 7·3) and 58·2kg (SD 7·3) respectively. There was no significant difference in age or weight between those women who had vault granulations and those who did not.

Presenting symptoms of patients with vault granulations. Only two patients denied any symptoms whereas most patients presented with a discharge or vaginal bleeding or both.

Discussion

Total abdominal hysterectomy leaves a vaginal vault wound in a closed, moist and essentially non-sterile environment to which an absorbable foreign body (suture) is added. Therefore, depending on it severity, the subsequent inflammatory reaction results in healing by secondary rather than primary intention, and this may result in the formation of vault granulations in some women. Estimates of the frequency of vault granulations vary widely: Howkins and Williams (1968) reported a rate of 37% after complete vault closure, and they suggested that this could be reduced by use of plain rather than chromic catgut; Fairlie and Al-Hassani (1973) closed the vault with the Lembert suture and reported a rate of 11% when catgut was employed and 3% when they used polyglycolic acid. Hence some of the standard texts on operative gynaecology (Howkins and Stallworthy 1974; Howkins and Hudson 1983) which address the issue advise the use of No. 0 plain catgut to minimize the occurrence of vault granulations. They are non-committal about whether the vault should be closed or left open, and about the exact closure technique.

In our postal survey on current UK practice on vaginal vault closure we found that most surgeons (60%) used No. 1 chromic catgut, fewer than 3% employ the Lembert suture and that most estimated the frequency of vault granulations at <20%. This probably reflects the fact that many procedures in gynaecological practice, and indeed in many areas of medicine in general, are a product of habit and upbringing and often fail to stand up to scientific scrutiny. It is therefore important and illuminating to ask one's colleagues and oneself questions about basic clinical practice, and helpful to think again about something that is done every day (Amias, 1987).

The logical progression from our postal survey was to mount a prospective, randomized study. We found that the frequency of vault granulations is indeed high (32%), that almost all (95%) were symptomatic and that chromic catgut was associated with significantly more granulations than polygalactide. Our postal survey had revealed that the most popular closure techniques were an interrupted mattress suture (54%) and a continuous suture (43%): it therefore seemed appropriate to compare these two. Although with both catgut and polygalactide, granulations occurred more often when a continuous suture was used, the difference between these two techniques was not statistically significant. This may reflect the fact that the number with vault granulations was small, and that it might require larger numbers to demonstrate a difference between the two. The alternative explanation is that these two closure techniques are theoretically unlikely to have a differential influence on the formation of vault granulations: both involve piercing the vaginal epithelium, and it may be the presence of the foreign material of the suture in the lumen of the vagina at the vaginal vault which results in healing by secondary intention and the formation in some women of vault granulations. If that is so, the logical comparison would be between a technique which involves piercing the vaginal epithelium and one which does not, such as the Lembert suture. A substantial number of gynaecologists (13% in our postal survey) leave the vaginal vault open at hysterectomy: it would also be interesting to establish whether this practice influences the occurrence of vault granulations and other complications such as pelvic haematoma. We have compared only the two most popular suture materials and closure techniques: more and more 'inert' suture materials are now on the market and studies to compare these should be undertaken as it seems likely that with the ideal combination of suture material and closure technique the frequency of vault granulations may be reduced to a bare minimum. Prophylactic antibiotics may also have a role to play.

Since vault granulations occurring after hysterectomy for benign causes are themselves benign, and since they are thought to regress spontaneously over a few months, some gynaecologists may opt not to treat them unless they are symptomatic. Our study showed that the vast majority (95%) are symptomatic. Although few women complain of bleeding at the 6 week postoperative review, this is probably because most women have not resumed intercourse at this time.

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Reproductive prognosis after abdominal metroplasty in bicornuate or septate uterus: a life table analysis

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Summary. Reproductive prognosis after abdominal metroplasty was assessed in 73 women with a septate and 71 with a bicornuate uterus who underwent metroplasty at the First Obstetric and Gynecologic Clinic of the University of Milan between 1972 and 1985. The overall cumulative 5-year delivery rates were respectively 70% and 73% in women with septate and bicornuate uterus, rising constantly with time. The number of previous miscarriages did not affect the reproductive prognosis: the 5-year probability of giving birth was 64% and 75% in the women with septate uterus and respectively fewer than two or two or more previous miscarriages, and the corresponding values were 66% and 73% in the bicornuate uterus subgroup. The miscarriage rate (about 20%) was similar with both types of malformation.

Bicornuate and septate uterus are the most frequent uterine Müllerian malformations (Buttram 1983). Although they can be asymptomatic, they may be associated with primary infertility and miscarriage in the first and second trimesters (Wallach 1972; Jones 1981) When this happens, a surgical procedure is generally indicated.

Live birth rates of 50–70% have been reported after metroplasty (McShane *et al.* 1983; Musich & Behrman 1978; Capraro *et al.* 1968; Rock & Jones 1977; Thompson *et al.* 1966; Heinonen *et al* 1982; Kaser 1981; Kusuda 1982), but published studies are based on small numbers of women, and generally provide scant data on the duration of follow-up. Moreover, there is uncertainty about the effect on prognosis of the various malformations, and few studies have investigated the relation between previous obstetric performance, the type of malformations and the results of surgery.

We analysed a consecutive series of 144 women with a bicornuate or septate uterus who underwent metroplasty at the First Obstetric and Gynecologic Clinic of the University of Milan.

Subjects and methods

Between 1972 and 1985, 73 women with sterility or recurrent miscarriage underwent metroplasty for septate uterus (six also had a vaginal septum) and 71 for bicornuate uterus (class V and IV respectively, according to Buttram and Gibbons's classification (Buttram 1983)) at the First Obstetric and Gynecologic Clinic of the University of Milan. Since the classification of Buttram and Gibbons does not define the minimum

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fundal indentation for a double uterus to be classified as bicornuate rather than septate, we defined as bicornuate an uterus with an indentation greater than 10 mm (Fedele *et al.* 1988).

Before surgery all the women had a hysterosalpingogram, urography, general assessment of health, a luteal phase endometrial biopsy, a glucose tolerance test and three progesterone and prolactin assays in the luteal phase plus one T3, T4, TSH, FT assay to exclude the presence of other diseases relevant to reproduction In couples with previous miscarriages, both the woman and her partner had their karyotype determined from peripheral leucocytes.

The women's ages, reproductive history at diagnosis (the number of previous miscarriages; none had had a term pregnancy) and the type of metroplasty are presented in Table 1.

Metroplasty was always performed with an atraumatic technique in an irrigated operating field with the aim of avoiding peritoneal adhesions. The myometrium was incised with an electric bistoury and accurate haemostasis obtained using a bipolar coagulator. Corticosteroids and antibiotics were given post-operatively as prophylaxis against adhesions.

After metroplasty women were instructed to avoid pregnancy for 3 months. When pregnancy occurred, regular medical examinations were offered, and each woman was advised to rest as much as possible and to avoid heavy work and travelling. Beta mimetic drugs were prescribed on clinical criteria after 15 weeks gestation. Cerclage was performed (in women with hysterosalpingographic diagnosis of cervical incompetence) between the 11 and 15 completed weeks gestation in 41 pregnancies (20 and 21 in women with septate and bicornuate uterus respectively) out of the 95 which reached 11 weeks. Elective caesarean section was generally chosen for delivery and was performed in 84 out of 95 pregnancies.

Table 1. Main characteristics of 71 women with a bicornuate uterus and 73 with a septate uterus, Milan 1972–1985

Characteristic	Bicornuate uterus ($n = 71$)		Septate uterus ($n = 73$)	
Age (years)	*n*	%	*n*	%
<25	5	(7)	7	(10)
25–29	32	(45)	30	(41)
30–34	27	(38)	20	(27)
>34	7	(10)	16	(22)
Previous miscarriage				
0	6	(9)	8	(11)
1	11	(16)	17	(23)
2	24	(34)	23	(32)
≥	30	(42)	25	(34)
Surgical procedures				
Tompkins	55	(78)	62	(85)
Jones	6	(9)	7	(10)
Te Linde	5	(7)	–	–
Strassman	5	(7)	4	(6)

There were two perinatal deaths associated with preterm birth (at 28 and 34 weeks gestation). In both, delivery was by elective caesarean section for intrauterine growth retardation. No fetal abnormality was observed in the pregnancies studied.

Data analysis

The cumulative proportion of women who became pregnant and gave birth was calculated by the product limit method and the curves were compared by the log-rank test (Peto *et al.* 1977) The event data used in computing the probability of becoming pregnant and giving birth to a child were the date of metroplasty, and respectively the date of the last period and the date of delivery.

Tests of statistical significance for contingency tables were based on usual χ^2 values, comparing observed and expected numbers of events and, where appropriate, on test for trend (Mantel 1963). The potential confounding effect of low birthweight, preterm birth, and other factors such as age and socio-economic status was controlled for using stratification and the Mantel-Haenszel procedure (Mantel & Haenszel, 1959).

Results

The cumulative 5-year proportion of women who became pregnant was 91% for septate and 93% for bicornuate uterus After 5 years respectively 70% (based on 45 births) and 73% (50 births) of women with septate and bicornuate uterus gave birth to a child, the frequency of delivery rising progressively with time.

The obstetric history was not associated with the reproductive prognosis. In women with a septate uterus the 5 years livebirth rate was 64% (based on 15 births) in the group with 0–1 previous miscarriages and 75% (30 births) in the women with two or more (χ^2_1 adjusted for age = 0·93, $P = 0·33$, Fig. 1). The respective

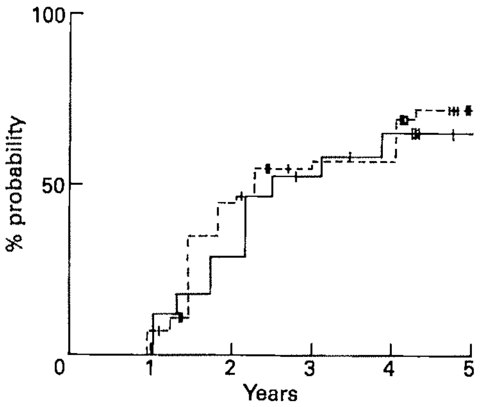

Fig. 1. Comparative 5-year probability of giving birth to a child according to obstetric history in 73 women with septate uterus. ———, Fewer than 2 previous miscarriages ($n = 25$); – – –, 2 or more previous miscarriages ($n = 48$); χ^2_1 adjusted for age 0·93, $P = 0{\cdot}33$). Milan, Italy 1972–1975.

values were 66% (based on 11 births) and 73% (39 births) when women with bicornuate uterus were considered (χ^2_1 adjusted for age = 0·26, $P = 0{\cdot}61$, Fig. 2). These estimates were largely unchanged when the analysis was restricted to women who did not undergo cervical cerclage (data not shown).

Likewise, miscarriage rates were similar with bicornuate and septate uterus. Sixteen miscarriages occurred in 66 pregnancies (24%) in women with bicornuate and in 11 of 56 (20%) with septate uterus. Age at diagnosis and reproductive history did not materially influence the frequency of miscarriage (data not shown).

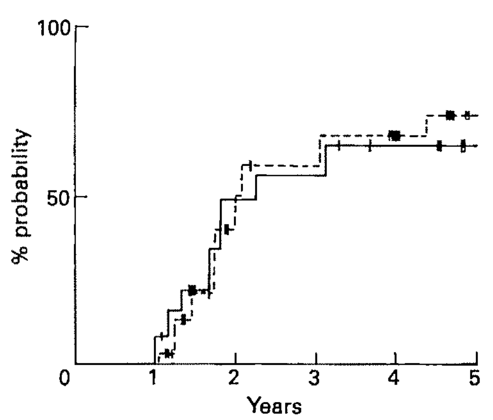

Fig. 2. Comparative 5-year probability of giving birth to a child according to obstetric history in 71 women with bicornuate uterus ———, Fewer than 2 previous miscarriages ($n = 17$); – – –, 2 or more previous miscarriages ($n = 54$); χ^2_1 adjusted for age 0 26, $P = 0{\cdot}61$). Milan, Italy 1972–1985.

The distribution of week at delivery and birthweight according to uterine malformation is set out in Table 2. No significant difference emerged in frequency of preterm births (<38 weeks gestation) or low birthweight.

Discussion

In this large series, women with Müllerian malformations had more than a 70% probability of giving birth to a child during the 5 years after metroplasty. This percentage was similar in women with bicornuate and septate uterus and was not influenced by their obstetric history.

These findings should not be greatly affected by bias. All women who underwent metroplasty in the study period were considered and none was lost to follow-up. Although the study period covered 13 years, the general clinical management did not change markedly and the surgical procedures were performed under the supervision of one of us (GBC). In this regard, analyses restricted to subdivisions of the time period did not show marked differences.

The major drawback of this study is the absence of a control group. Thus there is the possibility that the overall outcome might have been similar if these women had become pregnant without surgery. For example, Rock and Schlaff (1985) showed that of 70 patients diagnosed at the Mayo Clinic as having uterine malformations during the period 1953–1964, 83% of the 55 candidates for pregnancy bore living children without having had surgery An overall

Table 2. Birthweight and gestational week at delivery in 95 term pregnancies according to uterine malformation, Milan 1970–1985

	Bicornuate uterus ($n = 50$)		Septate uterus (n=45)	
Birthweight (g)*	n	(%)	n	(%)
<2500	10	(20)	6	(13)
2500<3500	31	(62)	34	(76)
≥3500	9	(18)	5	(11)
Gestational week at delivery†				
<38	12	(24)	7	(16)
≥38	38	(76)	38	(84)

*χ^2_1 trend adjusted for maternal age and week of gestation at delivery = 1·86, $P = 0{\cdot}17$.

† χ^2_1 adjusted for maternal age = 1·56, $P = 0{\cdot}21$.

short-term pregnancy rate of about 70% is similar to the rate observed in our institution and in the same period in a series of *sine causa* recurrent spontaneous miscarriages (Parazzini *et al.* 1988).

Our series included 42 women with primary sterility or a single miscarriage. The indication for metroplasty in this subgroup is controversial, we performed surgery because the uterine malformation was the only problem detected during thorough investigation and often because the woman was relatively old.

The live birth rate observed in this large series compares well with previous data. A study conducted in Boston on 14 women with poor reproductive histories who underwent a Tompkins metroplasty for a septate uterus reported 12 pregnancies and 10 viable infants within 2 years of surgery (McShane *et al.* 1983). Likewise Musich and Behrman (1978) studied 12 women with septate and 10 with bicornuate uteri, obtaining, respectively, six and four pregnancies after metroplasty. Similar findings were reported from the United States (Capraro *et al.* 1968; Rock & Jones 1977; Thompson *et al.* 1966) Finland (Heinonen *et al.* 1982), Switzerland (Kaser 1981) and Japan (Kusuda 1982), but in these series the type of double uterus was not specified.

It has been suggested that a bicornuate uterus is less frequently associated with repeated miscarriages than a septate one In our series the obstetric history was largely similar in the two subgroups. This may be at least partly explained by referral criteria; only women with previous miscarriages are generally diagnosed and referred for uterine malformation The finding of similar reproductive prognosis after metroplasty may have an anatomical explanation, since the post-surgical uterine cavity is similar for both malformations.

A surgical procedure may reduce fertility by creating pelvic adhesions. In our series, however, the cumulative 5-year proportion of women who became pregnant was more than 90% in both the septate and bicornuate uterus groups. This favourable finding is, at least partly, attributable to the routine precautions taken during surgery to avoid pelvic adhesions and to the type of operation most frequently performed. This was a Tompkins procedure, in which a single incision is made with a linear suture along the median sagittal plane of uterine body, that is, at the site considered at lowest risk of post-operative adhesions (Buttram & Reiter 1985).

In none of our patients did the metroplasty scar rupture. Eleven pregnancies ended in normal spontaneous labour and vaginal birth. Healing in a non pregnant uterus is probably better than healing after a cesarean section, because myometrial healing after a term delivery takes place in a uterus that is undergoing involution (Jones, 1981). Furthermore, to give the uterine incision the best possible opportunity to heal, our patients were instructed to avoid pregnancy for 3 months after metroplasty.

The frequencies of preterm birth and low birthweight were respectively 20% and 17% and were not affected by type of malformation or by cerclage. Although a high frequency of preterm birth has been reported in malformed uteri before metroplasty (Green & Harris, 1976), these percentages should be considered cautiously being, at least in part, attributable to the tendency to choose elective caesarean section as the mode of delivery.

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Maternal and paternal moderate daily alcohol consumption and unexplained miscarriages

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Summary. The relation between parental moderate alcohol consumption and the risk of miscarriage was analysed using data from a case-control study in Milan between January 1987 and June 1988. Cases were 94 women who had two or more 'unexplained' miscarriages (after exclusion of genetic, endocrine and Müllerian factors) and without full-term pregnancies, admitted or referred to the First Obstetric and Gynecologic Clinic of the University of Milan. A total of 176 women admitted for normal delivery on selected days to the same university clinic and without previous miscarriages were chosen as controls. Compared with non-drinkers the risk of recurrent miscarriage was 0·9 for regular drinkers. The point estimates were 0·9 for women reporting one drink per day and 0·8 for those reporting two or more. Compared with non-drinkers, the relative risk estimates for drinking by fathers were slightly above unity, being 1·7 for less than three drinks and 1·4 for three or more drinks per day, but the trend in risk was not statistically significant.

The association between excessive drinking throughout pregnancy and fetal growth, mental retardation and characteristic facial appearance ('fetal alcohol syndrome') is well recognized (Jones & Smith 1973; Clarren & Smith 1978). However, the role of moderate consumption on birthweight, stillbirth and mental behaviour is less clear (Little 1977, Quellette *et al.* 1977; Kaminski *et al.* 1978; Streissguth *et al.* 1983; Marbury *et al.* 1983; Sulaiman *et al.* 1988; Brooke *et al.* 1989). Miscarriages have been associated with moderate alcohol consumption, but the evidence is controversial and generally based on data from English speaking and North European populations, characterized by low levels of daily alcohol consumption (Harlap & Shiono 1980; Kline *et al.* 1980; Sokol *et al.* 1980; Halmesmäki *et al.* 1987). For example, in the UK survey reported by Wilson (1980) only about 8% of women drank 60–80 g alcohol a week and 3% 100–150 g and Halmesmaki *et al.* (1989) found that the average alcohol consumption of drinking women interviewed as controls in a Finnish case-control study of drinking and miscarriage was only 21 g/week. In these populations, even moderate drinkers may be selectively different from alcohol abstainers. Likewise, the potential role of paternal alcohol consumption in miscarriages is poorly understood, but it is

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known that alcohol intake may impair sperm production and motility (Vålimaki & Ylikahri 1983).

We have analysed the relation between alcohol intake and miscarriage using data from a case-control study on risk factors for recurrent miscarriages conducted in Northern Italy, where moderate alcohol consumption among women is a common and socially accepted habit.

Subjects and methods

Between January 1987 and June 1988, trained interviewers identified and questioned cases and controls using a standard questionnaire. Information was collected on personal characteristics and habits (i.e., smoking, coffee consumption), gynaecological and obstetric data and related medical history.

Questions on alcohol consumption included the number of days per week and the average number of drinks per day of each type of alcoholic beverage (wine, beer and spirits) consumed during the last pregnancy which miscarried for cases and in the first trimester of the index pregnancy for controls. The usual paternal alcohol consumption (number of days per week and average number of drinks per day) was also collected by interviewing only the women.

From these data the total daily average alcoholic beverage consumption was derived assuming a comparable pure alcohol content in each type of drink (125 ml of wine = 333 ml of beer = 30 ml of spirts = approximately 12 g of pure alcohol). Wine by itself accounted for more than 90% of alcohol consumption in men and in women in this population.

The cases included in the study were women without previous full-term pregnancies who had two or more 'unexplained' miscarriages during the first 3 months gestation, admitted or referred during the study period to the First Obstetric and Gynecology Clinic of the University of Milan. All miscarriages were confirmed by reviewing clinical records of the uterine curettage. A total of 94 cases, aged 25–39 years (median age 32) met these criteria: 67 women reported two miscarriages, 20 three and seven four or more. Within 6 months from the last miscarriage, all women had normal standard medical examination, hysterosalpingogram, luteal phase endometrial biopsy, glucose tolerance test, hormonal profile (three progesterone and prolactin assays in the luteal phase plus one T3, T4, TSH and FTI assay). Karyotypes from peripheral leucocytes of both partners were determined.

The control group was recruited from women who gave birth at term (>37 weeks gestation) to healthy infants on randomly selected days at the same university clinic. Women were specifically excluded if they reported a history of one or more miscarriage. A total of 176 control women aged 24–39 years (median age 29) were interviewed.

The cases were interviewed within 6 months of the last miscarriage and the controls were interviewed while in hospital for the delivery.

Data analysis

Odds ratios as estimators of relative risk (RR) (Breslow & Day 1980) of recurrent miscarriage together with their 95% confidence interval (CI) were computed from data stratified for age in quinquennia as described by Mantel & Haenszel (1959), and significance of linear trend in risk was based on the Mantel's extension test (Mantel 1963). The reciprocal potential confounding factors of maternal and paternal alcohol consumption and other factors (including smoking, coffee consumption and socioeconomic factors) were controlled using stratification and the Mantel-Haenszel procedure (Mantel & Haenszel 1959). However, since adjustment for these covariates did not materially change the relative risks, estimates adjusted for age only were chosen for presentation.

Results

The distribution of cases and controls according to age, parity of controls, education, smoking habits and coffee consumption is shown in Table 1. Controls were somewhat younger than cases (median age 29 *vs* 32 years). No association emerged between education and risk of miscarriage, but current smokers and coffee drinkers were at non significantly elevated risk (RR current smokers *vs* non smokers = 1·4 (95% CI 0·8 to 2·9); RR coffee drinkers *vs* non-drinkers = 1·4 (95% CI 0·7 to 2·6).

Table 2 shows the distribution of women with recurrent miscarriage and controls according to maternal and paternal daily alcohol consumption, together with the corresponding relative risk estimates. Compared with non-drinkers, the risk of recurrent miscarriage was 0·9 (95% CI 0·6

Table 1. Distribution of 94 women with recurrent miscarriage and 176 control subjects according to age, education and smoking habits. Milan, Italy 1987–1938

	Recurrent miscarriage (n = 94)		Control group (n = 176)	
	n	(%)	n	(%)
Age (years)				
<30	41	(43·6)	101	(57·4)
30–34	35	(37·2)	55	(31·3)
≥35	18	(19·1)	20	(11·4)
Parity				
0	94	(100·0)	92*	(52·3)
1	—	—	66	(37·5)
≥2	—	—	18	(10·2)
Education (years)				
<7	7	(7·4)	14	(8·0)
7–11	29	(30·9)	63	(35·8)
≥12	58	(61·7)	99	(56·3)
Smoking habits				
Ex-never smokers	59	(62·8)	124	(70·5)
Current smokers	35	(37·2)	52	(29·5)
Coffee consumption				
No	16	(17·0)	42	(23·9)
Yes	78	(83·0)	134	(76·1)

* Index pregnancy is not included.

to 1·5) for regular drinkers. The point estimates were 0·9 for drinkers of one drink per day and 0·8 for two or more (χ^2_1 trend = 0·11, P = 0·74). The relative risk estimates for a drinking father compared with a non-drinking one were slightly above unity, being 1·7 for less than three and 1·4 for three or more drinks per day, but the trend in risk was not statistically significant (χ^2_1 trend = 1·84, P = 0·17).

Discussion

The general finding of this study indicates that maternal and paternal moderate alcohol con-

Table 2. Relative risk of recurrent miscarriage according to maternal and paternal alcohol consumption. Milan, Italy 1987–1988

Mean no of drinks/day	Recurrent miscarriage (n = 94)*	Controls (n = 176)*	R.R † (95% CI)
Maternal			
Non drinkers	37	69	1‡
<2	26	51	0·9 (0·5–1·6)
≥2	29	56	0·8 (0·4–1·6)
χ^2_1 trend†			0·11 (P = 0·74)
Paternal			
Non drinkers	17	48	1‡
<3	19	27	1·7 (0·7–4·0)
≥3	58	97	1·4 (0·7–2·8)
χ^2_1 trend†			1·84 (P = 0·17)

* In some case the sum does not add up to the total because of missing values, † Adjusted for age; ‡ Reference category.

sumption is not associated with an increased risk of recurrent miscarriage. Although the number of cases was relatively limited, with this sample size it was still possible to exclude relative risks for maternal alcohol consumption above 1·6 for two or more drinks per day at the conventional 95% probability.

Selection is unlikely to account for the finding, since cases and controls were identified in the same institution and participation was almost complete. Allowance for several potential confounding covariates, including indicators of social status, smoking and coffee consumption, did not appreciably change the relative risk estimates. Recall bias should be more carefully considered. The assessment of alcohol consumption was based on self reporting and it is recognized that appreciable underestimating can occur (Chick *et al.* 1981). In Italy, however, moderate alochol consumption is socially accepted in women and men (ISTAT 1986; La Vecchia *et al.* 1987), recommendations to avoid alcohol in pregnancy have not received widespread attention and are not routinely advocated by gynaecologists. Although paternal intake was assessed by interviewing the woman only, this information is probably acceptable for the purpose of the classification adopted in this study. Further, the timing of data collection differs in cases and controls, but in both groups about 6 months elapsed between the first trimester of the index pregnancy and the interview.

These findings are consistent with most (but not all) other epidemiological studies. For example, no association between alcohol consumption and first trimester miscarriages emerged in a Finnish study by Halmesmäki *et al.* (1989) or in a Californian study by Harlap & Shiono (1980) although these authors reported an increased risk of second trimester miscarriage, but in another American study Kline *et al.* (1980) reported an approximately 2·5 increased risk of miscarriage in women drinking alcoholic beverages twice a week or more. The particular interest of our result lies, in our opinion, however, in the comparatively higher alcohol consumption observed in an Italian population, particularly by women.

Alcohol consumption impairs human sperm (Välimaki & Ylikahri, 1983) and animal data have shown that ethanol can induce chromosomal aberrations (Brown *et al.* 1979; Kaufman 1983). In our series, estimated relative risks of recurrent miscarriages were slightly, but not significantly, above unity for alcohol drinking men but no trend with intake was observed. Our findings agree with Halmesmäki *et al.* (1989) who found no relation between paternal alcohol consumption and miscarriage in a Finnish case-control study of 80 women. In conclusion, on the basis of these results and previous studies, there is convincing evidence that moderate maternal and paternal alcohol drinking is unlikely markedly to influence abortion rates.

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Malignant trophoblastic tumours in Norway. Fertility rate after chemotherapy

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Summary. During the period 1970–1986, 73 women with malignant trophoblastic tumours were reported in Norway. Forty-six of these women were sent a questionnaire about the course of pregnancies subsequent to treatment with methotrexate and actinomycin D. Only 30 of these women had had the desire to get pregnant; 10 had had one, 13 had had two, and six had had three further children. It is concluded that treatment with combination of methotrexate and actinomycin D is safe in terms of preserving fertility.

Women with malignant trophoblastic tumours are mostly in their reproductive years. As the prognosis is excellent after chemotherapy (Kolstad & Hognestad 1965) the women may later want to get pregnant. Some cytotoxic drugs may reduce fertility and there is interest in obtaining information about the fertility rate after the treatment. The purpose of this paper is to present the obstetric histories of a Norwegian population after the effective chemotherapy of invasive trophoblastic tumours.

Patients and methods

During the 17-year-period 1970–1986, 73 women with malignant trophoblastic tumours were treated in Norway. All were treated at the Department of Gynecologic Oncology at the Norwegian Radium Hospital. Fifty had an invasive mole, and the remaining 23 had choriocarcinoma.

Eight women were treated with high-dose methotrexate (vincristine, methotrexate, actinomycin D, cyclophosphamide, and leucovorin), while 65 were treated with sequential methotrexate and actinomycin D (methotrexate 25 mg intramuscularly daily for 4 days and actinomycin D 0·5 mg intravenously daily for 4 days).

The women were urged to avoid pregnancy for 2 years after the treatment, during which time serum human chorionic gonadotrophin (hCG) was estimated regularly. Half of the women used oral contraception during the 2-year observation period.

Hysterectomy was performed in 13 women, mainly because of severe bleeding. Five patients died from the disease. Nine were ⩾50 years of age when the disease was detected. The remaining 46 women were sent a questionnaire in February 1989. The questionnaire was returned by all but three. The three women who did not return the questionnaire are alive according to Central Cancer Register. The questions focused on their desire to get pregnant, use of contraceptives, number of deliveries, miscarriages and legal abortions, ectopic pregnancies, complications during pregnancy and delivery and mode of delivery. The median age for the 43 women when treatment started was 26 years (14–42 years) and they constitute our study group. Two of these women were from the group of eight who had received high dose methotrexate.

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Results

Thirteen of the 43 women had no desire to become pregnant and consequently used contraception beyond the 2 years. However, two of these women became pregnant unintentionally and had legal abortions. The other 30 women wanted to get pregnant. Of these one had not conceived during the 6 months between discontinuation of contraception and the completion of the questionnaire. Of the remaining 29 women, 10 had had one child, 13 had had two children, and six had had three children, a total of 54 children. All the children are alive and none has a congenital malformation. The period fertility rate among the women with previous invasive mole or choriocarcinoma was thus 1·8–1·9 per woman, which corresponds to the normal Norwegian population (Skjeldestad 1986).

Twelve of the children were born by caesarean section. The reason for this high number was partly fear of complications consequent on the previous trophoblastic disease. Furthermore three children were born preterm and one woman developed pregnancy hypertension. The other pregnancies were uneventful. In addition to the successful pregnancies there were six miscarriages, one mole and one ectopic pregnancy. Of the women treated with high-dose methotrexate one had one child and the other had used oral contraception. One woman had a retained placenta but placenta accreta did not occur.

Discussion

Rustin *et al.* (1984) found that the conception rate was 97% for women treated with methotrexate alone, but with combination therapy that included cyclophosphamide only 79% conceived. Women who were treated with three or more cytotoxic drugs, as well as women who received actinomycin D were less likely to conceive. This adverse effect of actinomycin D could not be demonstrated in the present or other studies (Hsieh *et al* 1985; Song *et al.* 1988).

In our study, 98% of the women who wished to conceive had at least one child. The one woman who had not had a pregnancy, which could bring the percentage up to 100, had been trying to conceive for only 6 months. Previous studies have reported infertility rates of 2·5–16% (Goldstein *et al.* 1984; Ngan *et al.* 1988; Rustin *et al.* 1984; Walden *et al.* 1976).

Our study did not demonstrate any increased risk of miscarriage (10% of all conceptions ended in miscarriage) but it is not powerful enough to detect a modest change. This figure is in accordance with the prevalence of miscarriage in the Norwegian population as a whole (9·8%), if induced abortions are excluded, (F. E. Skjeldestad, personal information). Other studies have reached the same conclusion (Rustin *et al.* 1984; Song *et al.* 1988), although the frequency of miscarriage in their study groups was somewhat higher.

Methotrexate has been shown to induce chromosomal aberrations in the preovulatory phase of oogenesis in mice (Goldstein *et al.* 1984), but all the children in our study were normal However, Van Thiel *et al.* (1970) have reported that most of the mutations are recessive and may not be detected in the first generation.

Different opinions exist as to when women should become pregnant after treatment. Bagshawe (1976) reported that trophoblastic disease relapsed in 9% up to 14 months after a full course of chemotherapy. Hörmann (1975) recommended an interval of 3 years. In our study the average time interval from the completion of chemotherapy to the first conception was approximately 3 years and resulted in no complications.

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No effect of intralesional injection of interferon on moderate cervical intraepithelial neoplasia

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Summary. Women with histologically confirmed cervical intraepithelial neoplasia grade 2 (CIN 2) were treated in a double blind investigation of treatment with intralesioneal interferon alpha-2b (Intron a). Before treatment commenced, the existence and the types of human papillomavirus (HPV) were assessed in [^{35}S] methionine-labelled cervical biopsies by the determination of specific protein markers. Pronounced side effects occurred in all the women treated with interferon and the trial was stopped when it became apparent that there were no obvious beneficial effects. No positive benefits of interferon treatment were detected on either the CIN 2 or on the persistence of HPV types. It is concluded that intralesioneal injection of interferon has no place in the treatment of CIN.

There is a strong evidence implicating human papillomavirus (HPV) in the development of cervical intraepithelial neoplasia (CIN) (Gissman 1984, Syrjänen 1984, zur Hausen, 1986), although a direct aetiological effect has been questioned (Murdoch *et al.* 1988, Ward *et al.* 1989, Tidy *et al.* 1989).

Interferon possesses both anti-neoplastic and antiviral properties (Strander 1986) and, thus, it seemed reasonable to expect that this drug would induce beneficial changes in CIN. Indeed, beneficial effects on CIN after local treatment with interferon have been reported (Møller *et al.* 1983, De Palo *et al.* 1985, Choo *et al.* 1986). However, other reports described disappointing results (Byrne *et al.* 1986, Krause *et al.* 1987). Different methods of application of interferon in these studies and a possible type specific antiviral effect of interferon might explain these differences.

The aims of the present study were to investigate whether interferon alpha-2b can induce regression of CIN 2, or cause the reduction or disappearance of some or all types of the virus.

Intralesioneal treatment was chosen because a previous report had suggested promising results with this method of application (Choo *et al.* 1986).

Patients and methods

The study was approved by the local ethics committee. After giving informed consent women with CIN 2 were enrolled in the study. The diagnosis of CIN 2 was made by repeated cytology and colposcopy, and only those with consistent

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findings participated in the study. Exclusion criteria included: pregnancy and coinfection with herpes genitalis virus, *Neisseria gonorrhoea* and *Chlamydia trachomatis*. Blood samples were obtained for determination of lactate dehydrogenase, haemoglobin, leucocytes, platelets and alkaline phosphatase because of the possible influence of interferon on these factors.

The participants were allocated to treatment with placebo or interferon by the method of sealed envelopes. Randomization was in blocks. The study was double-blind because it was not possible to distinguish between the interferon and placebo solutions

Therapy began within one month after the diagnosis had been confirmed. Colposcopically guided biopies were obtained from the vaginal surface of the cervix before start of treatment. The biopsy was divided, one piece was taken for histological investigation, and the other was placed into sterile transport medium (DMEM containing 5% human serum, 300 units/ml penicillin, 300 g/ml streptomycin, 7·5 g/ml Fungizone) for HPV type determination.

The histological investigation confirmed the initial diagnosis reached by cytology and colposcopy in every woman

The assessment of the HPV type was based upon determination of marker proteins in high resolution two dimensional gels prepared from [^{35}S] methionine-labelled cervical biopsies. This has been shown to provide an alternative and easier method with a higher sensitivity than identification of HPV DNA type by hybridization on filters or tissue sections. The method is described in detail elsewhere (Fey *et al.* 1986, Mose Larsen *et al.* 1989). In short, after colposcopically directed extirpation, cervical biopsies were labelled with [^{35}S] methionine by incubation in a medium for 20 h. The biopsy was then homogenized, treated with DNAse and RNAse, and the proteins separated by two-dimensional gel electrophoresis. The resulting fluorograms were compared against standard patterns and the position of the HPV-type specific protein was used to assign HPV type.

Human serum albumin was added to the saline solution to make it indistinguishable from the interferon-saline solution. Either 1 ml of a saline solution containing 2 × 10^6 IU interferon alpha-2b (Intron a) (Essex Pharma) or 1 ml of a saline solution containing human albumin were injected twice weekly for 5 weeks. The injections were guided through the colposcope and made at four sites into areas of abnormality.

Four months after the last injection the patients were assessed again by colposcopy, cervical curettage, cytological smears and by cervical biopsies which were investigated both histologically and for HPV type.

Systemic and local side effects were monitored during the treatment.

Statistics

Choo *et al.* (1986) reported a cure rate with interferon treatment of 90%. Less optimistic, we expected a cure (disappearance of both virus and CIN) in about 60% in the interferon group. Spontaneous regression of CIN may occur, although very different rates have been reported (for a discussion see Syrjänen *et al.* 1985). How-

Table 1. HPV types in cervical biopsies showing CIN 2 before and after intralesioneal treatment with interferon alpha-2b or placebo.

		Type of HPV	
Patient	Treatment	Before treatment	After treatment
1	Interferon	18,16	18,16
2	Placebo	6	6
3	Placebo	16	16
4	Interferon	31	31
5	Placebo	11	11,16
6	Interferon	16,18	11,18
7	Placebo	11,6	—
8	Interferon	16	16
9	Interferon	16	16
10*	Interferon	31	-

*Excluded because of intolerable side effects ever, within four months the spontaneous regression rate is no more than 10—20%. Thus, we estimated, in order to detect a change of 50% with a type 1 error of 5% and a type 2 error of 20% that 20 patients were needed in each group.

Results

Although statistical considerations had suggested that a minimum of 40 women would be needed for the study, only 10 women all with CIN 2 had entered the study before it was stopped for ethical reasons: six had been treated with interferon and four with placebo. The two groups were similar for age (interferon: mean 32·3, range 29–46; placebo: mean 31·3, range 28–34), parity (50% nulliparous in each group) and marital status (one woman in each group was unmarried).

HPV was demonstrated in the cervical biopsy in eight of the 10 women both before and after the treatment period. As would be expected there was a high proportion of HPV types 16, 18, and 31 in the lesions investigated. The types of HPV found before and after treatment are shown in Table 1, treatment had little effect on the HPV types found in the biopsies. Semiquantitive determination of HPV-type-specific proteins showed that the amount of virus remained unaffected.

The results of reassessment after 4 months and the subsequent therapy are shown in Table 2. Complete regression of the CIN 2 was seen in one patient treated with interferon and partial regression in one patient in each treatment group. Two women treated with interferon and one treated with placebo progressed to CIN 3. One woman was excluded during the study because of unacceptable side effects and could not be assessed. The diagnosis of CIN remained the same after the treatment in one interferon and two placebo treated patients.

None of the placebo-treated but all women treated with interferon complained of severe side effects during the treatment. All the interferon treated women experienced fever, fatigue, headache, arthralgia and myoalgia from 2 h after the injection and lasting 4–8 h. The adverse effects occurred after each treatment without any decline in the severity. No changes were observed in any of the factors measured in the blood.

A review of the first ten patients showed that interferon treatment had no effect on CIN nor on the existence of HPV regardless of initial type. We decided to stop the trial because of the adverse side effects. Consequently, the study proved to be very small and the lack of effect observed does not rule out some benefit from interferon. However, the difference between the proportions of patients cured was $(1/6-0/4) = 0{\cdot}167$. If no difference between interferon and placebo the standard error of the proportion difference can be estimated to the square root of $(1/10*(1-1/10)*(1/6+1/4)) = 0{\cdot}194$. Thus, the 95% confidence interval for the true difference between proportions cured is $0{\cdot}167 \pm (1{\cdot}96 \times 0{\cdot}194) = -0{\cdot}213$ to $0{\cdot}546$, showing that interferon had little effect.

Discussion

There is growing recognition that human papilloma virus plays a role in the development of cervical neoplasia (McCane 1988) and it might be expected that the antiviral activity of interferon

Table 2. Colposcopic, cytological and histological findings in women with CIN 2 after treatment with interferon alpha-2b or placebo and histology.

Patient no	Treatment	Colpo	Cyt	Hist	Therapy	Cone histology
1	Interferon	Normal	Normal	Normal	Control	
2	Placebo	CIN 1	CIN 2	CIN 2	Cryo	
3	Placebo	CIN 2	CIN 2	CIN 2	Cryo	
4	Interferon	CIN 1	CIN 1	CIN 3	Cryo	
5	Placebo	CIN 1	CIN 2	CIN 3	Cone	CIN 3
6	Interferon	Normal	CIN 2	CIN 3	Cone	CIN 3
7	Placebo	CIN 3	CIN 3	CIN 3	Cone	CIN 3
8	Interferon	CIN 2	CIN 3	CIN 2	Cryo	
9	Interferon	Normal	CIN 1	CIN 1	Control	
10*	Interferon	–	–	–	–	

*Excluded because of intolerable side effects. Colpo = colposcopical diagnosis: cyt = cytological diagnosis of smears; hist = histological diagnosis of cervical biopsies.

would prove of some value in inhibiting the development of such lesions. Interferon has been shown to have specific antitumour effects (Strander 1986) and a positive effect in the treatment of benign condyloma acuminata (Gall *et al.* 1985, Eron *et al.* 1986). However, there is uncertainty concerning the treatment of the HPV-associated premalignant CIN; Møller *et al.* (1983), De Palo *et al.* (1985) and Choo *et al.* (1986) have reported positive effects, but these studies were all uncontrolled. On the other hand, an uncontrolled (Krause *et al.* 1987) and one placebo controlled (Byrne *et al.* 1986) trial failed to show any effects of interferon on CIN. Byrne *et al.* (1986) applied interferon dispersed in a gel with a cervical cap and the authors suggested that inadequate penetration of the drug through the dysplastic epithelium might partly explain the lack of effect. Choo *et al.* (1986) used intralesioneal injections, but their patients were assessed only by colposcopy and cytology as these authors considered that taking biopsies from the cervix might induce the regression of CIN (Jordan *et al.* 1984). In the present study we used intralesioneal injections but observed no beneficial effects. The cervical biopsies in our study did not induce regression of CIN.

The cytological and histological findings were concordant before treatment but discrepancies were recorded after treatment. This has been observed before and Krause *et al.* (1987) suggested that local interferon treatment may alter the exfoliation of dyskaryotic cells and blur the vascular pattern, thus making further assessment by smears and colposcopy unreliable.

There is some evidence to suggest that different HPV types have different sensitivities to interferon. HPV types 6 and 11 are almost exclusively found in benign condyloma acuminata and these lesions exhibit a high response rate to intralesioneal interferon (Gall *et al.* 1985, Geffen *et al.* 1985). Schneider *et al.* (1987), in an uncontrolled trial of the treatment of condyloma acuminata and CIN, observed that the response rate to interferon was less in the presence of HPV types 16/18 than with HPV types 6/11. However, with condyloma acuminata, HPV types 16/18 were not found and the disorder rather than the HPV type might explain the difference in response. In accordance with other workers (Byrne *et al.* 1986, Schneider *et al.* 1987, Murduch *et al.* 1988) we detected HPV types 16, 18 and 31 in a high proportion (80%) of the CIN 2 lesions investigated. By chance, all the lesions treated with interferon contained at least one of these types. In our study, interferon had no effect on the persistence of these virus types, confirming the observations of Schneider *et al.* (1987). It is impossible to clarify the effects of interferon on other HPV types from our study

One possible conclusion from our study is that CIN did not regress because the virus infection was still active. However, it is more likely that interferon had neither anti-HPV type 16, 18 and 31 nor antineoplastic properties, at least with application route used. Our results agree with Byrne *et al.* (1986) and Krause *et al.* (1987) who used a non-invasive local application of interferon.

We consider that the absence of obvious therapeutic benefit and the pronounced side effects establish that interferon has no place in the treatment of CIN.

Acknowledgments

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Imaging in acute fatty liver of pregnancy. Case report

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Case report

A 30-year-old woman presented at 36 weeks gestation in her fifth pregnancy with a one day history of vomiting, abdominal pain and jaundice. She had previously used combined oral contraceptives without side effects and there was no history of liver disease, drug ingestion, alcohol abuse or risk factors for viral hepatitis. She had one first trimester miscarriage and, apart from a retained placenta on two occasions, her pregnancies had been uncomplicated.

On admission she was apyrexial and normotensive, with no generalized oedema or proteinuria. She was mildly jaundiced and had five spider naevi but there were no other stigmata of chronic liver disease or signs of hepatic encephalopathy. There was no hepatomegaly, the fundal height was consistent with dates and the membranes were intact.

Liver function tests (LFTs) were abnormal, with raised bilirubin (79 μmol/l; N 0–17), aspartate aminotransferase (327 IU/l; N 5–45), alkaline phosphatase (489 IV/l; N 30–115) and uric acid (0·48 mmol/l; N 0·10–0·36). Her serum albumin was 34 g/l (N 35–50). Full blood count was normal (haemoglobin 13·8 g/dl, WBC 9·8 × 10^9/l, and platelets 191 × 10^9/l) but clotting was abnormal with a prothrombin time of 51 s (control 14).

At no time was she hypertensive nor was there any significant proteinuria. Her clinical condition initially improved after treatment with intravenous fluids and fresh frozen plasma. The differential diagnosis of her hepatic failure lay between acute fatty liver of pregnancy (AFLP) and viral hepatitis (non-A, non-B). Abdominal ultrasound using a 5 MHz curved linear array transducer showed no gallstones or evidence of obstruction and the liver appeared normal. Subsequent investigations showed no serological evidence of hepatitis A or B, or cytomegalovirus.

Using a high resolution scanner (Phillips TX), a single 10 mm CT section was performed through the upper abdomen. The density of the liver was uniformly low (18·7 Hounsfield Units (HU); normal range 50–75) and a diagnosis of AFLP was made. Liver biopsy was not performed because of her coagulopathy.

At this stage, 2 days after admission, her liver function tests and her general condition deteriorated, with vomiting and signs of hepatic encephalopathy. Induction of labour was planned but she went into labour spontaneously overnight. Fresh frozen plasma was given during the second stage and she had a spontaneous vaginal delivery of a healthy daughter. The placenta was retained and manual removal was performed without anaesthesia or complications. There was no postpartum haemorrhage, the total blood loss being 400 ml.

Subsequently, liver function improved (Fig. 1) and repeat CT scan 13 days later demonstrated marked improvement in liver density (49·7 HU). At this point clotting had improved sufficiently to permit a liver biopsy but she

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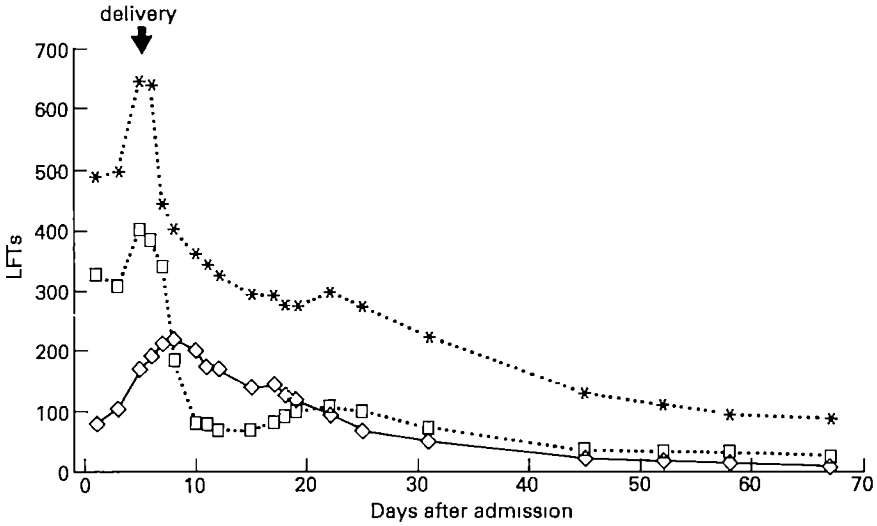

Fig. 1. Liver function tests (LFTs) before and after delivery —◇— bilirubin (μmol/l), ---□--- aspartate (IU/l); —*— alkaline phosphatase (IU/l).

declined this. Five weeks after delivery her liver function tests were normal, autoantibodies were negative, and there was no serological evidence of recent viral infection with hepatitis A or B, cytomegalovirus, or Epstein-Barr virus. A further liver scan at this time showed a normal density (62·9 HU).

Discussion

Jaundice in the third trimester is a diagnostic problem. Early diagnosis of AFLP is important as early delivery appears to improve the prognosis, whereas it is best avoided in the acute phase of viral hepatitis. Biochemical liver function tests are non-specific and serology for viral hepatitis can, in practice, take valuable time. Liver biopsy is often precluded because of coagulopathy.

Whether ultrasound or CT scanning is the best method of detecting fatty infiltration is debatable. In non-pregnant patients with alcohol related steatosis, ultrasound has both a high specificity and sensitivity especially in severe cases (Bydder *et al.* 1980, Campillo *et al* 1986, Kissin *et al.* 1986, Saverymutta *et al.* 1986). However, Meek *et al.* (1984) suggested that, at least in non-pregnant patients, CT scanning is more sensitive than ultrasound, detecting fatty infiltration correctly in 9 of 14 by CT scanning and in 1 of 11 by ultrasound. To date we have traced only one case report showing the value of CT scanning in the diagnosis of AFLP (McKee *et al.* 1986). In our patient an ultrasound scan showed no abnormality whilst CT scanning was abnormal, supporting the use of CT scanning for the diagnosis of AFLP when liver biopsy is precluded.

This case report demonstrates that CT scanning may be helpful in establishing the diagnosis of AFLP. Ultrasound may be useful in identifying other causes of jaundice in the third trimester as well as AFLP, so should remain the first line investigation. However, a normal ultrasound scan does not exclude AFLP and we recommend performing a CT scan in cases where the diagnosis is unclear.

CT scanning is readily performed, it is non-invasive and provides a rapid result. Phantom tests on our scanner give an estimated skin dose of 80 mSv for a single 10 mm section, so the radiation dose is low and acceptable in the circumstances.

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Simultaneous intrauterine and cervical pregnancies after in vitro fertilization and embryo transfer in a patient with a history of a previous cervical pregnancy. Case report

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Case report

We report simultaneous intrauterine and cervical pregnancies occurring after *in vitro* fertilization and embryo transfer (IVF-ET) in a 30-year-old woman with a history of a natural cervical pregnancy.

She was initially seen at St Mary's Hospital, Newport, Isle of Wight in March 1983, complaining of post-coital bleeding. There was a cervical ectropion, with normal cervical cytology. Treatment by cervical dilatation, curettage of the uterine cavity and cautery to the cervix was undertaken. No other abnormality was found and at follow-up the cervix appeared healthy.

The next admission was as an emergency in November 1984, with acute lower abdominal pain. At laparoscopy the patient was found to have a haemoperitoneum resulting from a ruptured right ampullary ectopic pregnancy. A right salpingectomy was performed. The left fallopian tube and ovary were noted to be normal.

The patient was seen again in March, 1985, at the request of her general practitioner. Following a very light period she had further slight vaginal bleeding 2 weeks later. In addition her general practitioner had been concerned about the appearance of her cervix. There was no abnormality on abdominal palpation. On speculum examination however, the cervix was ballooning with prominent blood vessels coursing over the surface. The external cervical os was pin hole in appearance.

At examination under anaesthesia for evacuation of a presumed cervical ectopic pregnancy, there was a partly solid, partly cystic mass replacing the cervix. This was evacuated digitally leaving a freely bleeding cervical cavity. The internal cervical os was found to be closed. Dilatation and uterine curettage was performed. Several catgut sutures to the cervix, and firm vaginal packing were necessary to arrest the haemorrhage. Post-operative recovery was uneventful. Histology confirmed a cervical pregnancy.

At review 6 weeks after discharge the cervix appeared normal. There had been one normal menstrual period, and no abnormal loss. She was advised that she could try to conceive again.

After failure to conceive for 12 months, she was seen again in April, 1986. Results of routine infertility investigations were normal. A repeat laparoscopy confirmed the patency of her left tube. The cervix appeared normal, and was easily dilated to 8 Hegar. After a further 18 months secondary infertility she was referred to the regional sub-fertility clinic at the Princess Anne Hospital, Southampton, for a second opinion. In January 1988, a diagnosis of possible cervical stenosis prompted a further cervical dilatation to be performed. At operation, the external cervical os was pinpoint, but dilated readily to 7 Hegar, and then with more force to 10 Hegar.

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In June 1988, she participated in the Southampton University IVF programme. Eleven oocytes were retrieved, of which nine fertilized, resulting in the transfer of three embryos into the uterus without difficulty. This attempt failed and was followed by an unsuccessful transfer of three cryo-preserved embryos.

She started her second IVF-ET treatment cycle in May 1989. She was treated with buserelin nasal spray to down-regulate the pituitary gland before ovarian stimulation with human menopausal gonadotrophin. Oocyte maturation was achieved with human chorionic gonadotrophin and 16 oocytes were retrieved by the transvaginal route. Twelve oocytes fertilized and 48 h later three embryos were transfered to the uterus. The transfer was easily performed using a Bourne embryo transfer catheter with an end opening (Wallace, UK).

Twelve days after embryo transfer, the patient had vaginal bleeding of 4 days duration. This was assumed to be a normal period and that the cycle had once again been a failure. To help recover she went on holiday. Twelve days after the period had ceased she had further minimal vaginal bleeding followed by a further heavier bleed 6 days later when she was admitted to the local hospital. An ultrasound examination was not performed on this admission but a urinary pregnancy test proved positive. The bleeding settled spontaneously and after discussion between the admitting gynaecologist and the Southampton IVF unit, the patient returned to be assessed in the IVF clinic.

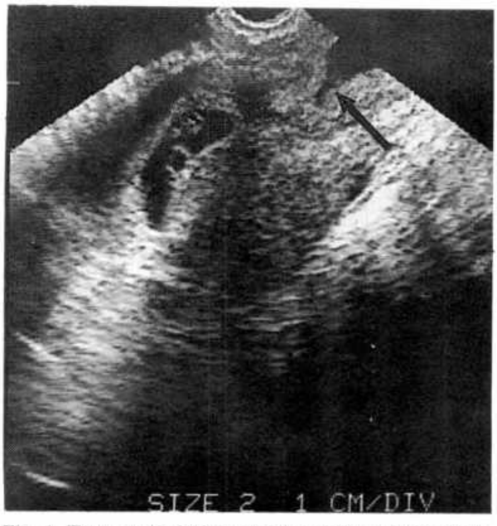

Fig. 1. Transvaginal ultrasound sagittal section of the intrauterine pregnancy at 7 weeks gestation. Arrow shows the level of the internal cervical os with the proximal part of the cervical gestation sac visible.

Transvaginal ultrasonography showed two gestation sacs, one intrauterine (Fig. 1) and one clearly in the cervix (Figs. 1 & 2). Both fetal heart beats were identified, and both crown rump lengths were 10mm corresponding to 7 weeks gestation.

She was admitted immediately to The Princess Anne Hospital for assessment and transvaginal ultrasound scans were performed periodically during her stay (Fig. 3). She had further bleeding 3 weeks after admission and transabdominal ultrasonography was performed to avoid direct pressure on the cervix. The scan showed both fetal heart beats to be present. Shortly afterward she started to bleed and became clinically shocked. An immediate blood transfusion was given and arrangements for evacuation of the uterus were made.

At operation the external cervical os was open and a fetus was partially extruded through the cervix. Digital evacuation of the cavity was performed. The cervical walls were thin, ragged and bleeding profusely. The internal os was easily seen, being 4 mm dilated. Haemostasis was achieved by cervical cerclage with merselene tape at the level of the internal os. The vagina was firmly packed and a urethral catheter was inserted. Blood loss before and during the procedure was estimated at 1·5 litres. A total of 4 units of blood were initially transfused. The post-operative haemoglobin was 9·8 g/dl and a further 2 units of blood was subsequently trans-

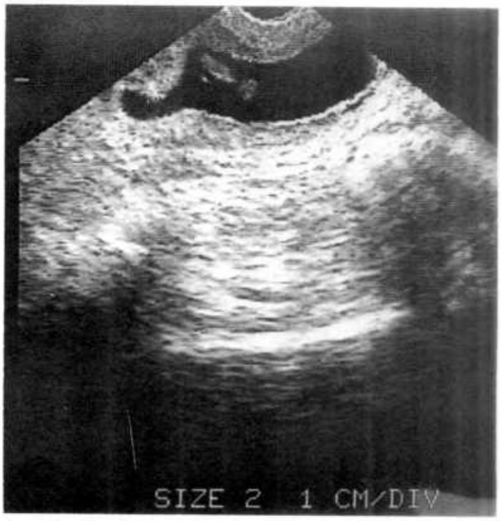

Fig. 2. Transvaginal ultrasound sagittal section of the cervical pregnancy at 7 weeks gestation.

fused. The pack and catheter were removed 48 h later, and no further vaginal bleeding or post-operative complication occurred.

One week later a transvaginal ultrasound scan showed that the intrauterine pregnancy was still viable. The fetal crown rump length was 46 mm corresponding to a 11+ weeks gestation. The patient was discharged from hospital 3 days later. Her haemaglobin was 12.1 g/dl.

Two weeks later, on July 23, 1989, she was admitted to St Mary's Hospital, Isle of Wight, with a 72-h history of lower abdominal and loin pain and a pyrexia of 40°C. A diagnosis of acute pyelonephritis was made a subsequently confirmed by urine culture. She was given broad spectrum antibiotics and her condition improved. Unfortunately 3 days later, at 13½ weeks gestation, heavy vaginal bleeding occurred. A transabdominal ultrasound showed a 13-week fetus with an absent heart beat. Removal of the cervical suture and evacuation of the uterine contents were performed the same day. Following a significant haemorrhage during the procedure, a 6 unit blood transfusion was required post-operatively.

Ten weeks later the patient required a further dilatation and curettage after persistent irregular vaginal bleeding. At this procedure the cervix was entirely normal in appearance.

Discussion

The true incidence of naturally occurring cervical ectopic pregnancy is uncertain, but has been reported as between 1 in 1000 to 1 in 95 000 (Hofmann *et al.* 1987). Tubal ectopic pregnancy is a well-recognized complication of IVF-ET or GIFT (gamete intra-fallopian transfer) and has a reported incidence of between 1·8% and 13·2% of such assisted pregnancies (Cohen *et al.* 1986). Two other cervical ectopic pregnancies after IVF-ET have been reported (Bayati *et al.* 1989, Weyerman *et al.* 1989). As far as we know ours is the first report of a recurrent cervical pregnancy.

Structural anomalies of the uterine corpus and cervix, leiomyomata, intrauterine contraceptive devices, previous termination of pregnancy, chronic endometritis, cervical dilatation and uterine curettage have been implicated as possible predisposing factors (Dicker *et al.* 1985). Our patient had had a dilatation and curettage before her first cervical pregnancy, but otherwise had no other contributory factors. It is possible that the resultant structural damage due to the first cervical ectopic pregnancy may have caused a permanent alteration to the uterine anatomy at the level of the internal os.

The use of transabdominal ultrasonography to diagnose cervical pregnancy was first reported by Raskin (1978). There have been fewer than a dozen reports since. The present report may be the first embryonic cervical pregnancy to be identified initially by transvaginal ultrasonography, with further observations over several weeks. Bayati *et al.* (1989) found vaginal ultrasound unhelpful in the diagnosis of their case, and Weyerman *et al.* (1989) failed to make the diagnosis until 16 weeks gestation. The quality of the images obtained with a high resolution (7·5 MHz) transvaginal ultrasound probe (Bruel & Kjaer, Denmark) can be seen in Figs 1–3, and makes the diagnosis beyond doubt. As a comparison we performed transabdominal ultrasound examination (3.5 MHz curvilinear array probe) at 7 weeks gestation. However, with a full bladder, the cervix was poorly imaged and the gestation sac which we knew to be present, could not be positively identified.

Due to this patient's history of infertility and the additional complication of a viable intrauterine pregnancy, we attempted to be as conservative as possible in our management. It was decided that evacuation of the cervical pregnancy should be performed soon after fetal death was diagnosed, or when miscarriage became inevitable, in the hope that the con-

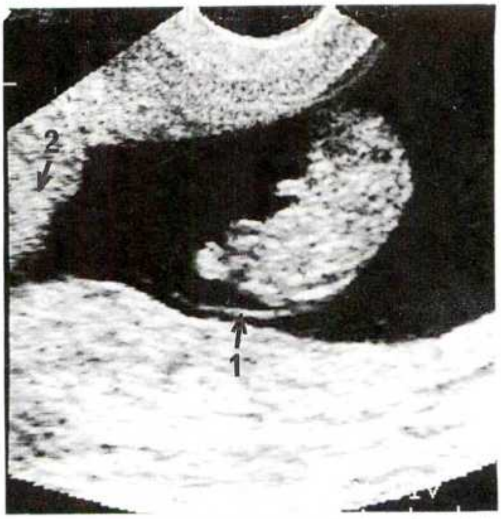

Fig. 3. Transvaginal ultrasound sagittal section of the cervical pregnancy at 9 weeks gestation. Arrow 1 indicates the umbilical cord, arrow 2 the placenta in a supero-anterior position at the level of the internal os.

sequent constriction of the placental bed blood vessels would help to reduce the risk of haemorrhage.

Conservative management by cervical cerclage was first described by Woodforde Scott *et al.* (1978), who used a polythene sucker tube as a cervical obturator. The techniques was subsequently used successfully in two further cases (Bernstein *et al.* 1981), where haemostasis was achieved with a McDonald type cervical suture and vaginal packing.

Our patient, aware that the risk of uncontrollable haemorrhage might necessitate a hysterectomy, requested that every chance of survival was to be given to the intrauterine pregnancy. She was kept under constant observation in hospital after the diagnosis of the intrauterine and cervical pregnancies and frequent ultrasound examinations were performed to monitor fetal viability. Six units of cross-matched blood were kept permanently available. Following the procedure to deal with the cervical pregnancy the intrauterine pregnancy appeared undisturbed and remained viable for a further 3 weeks Unfortunately a subsequent urinary tract infection may have contributed to the loss of the surviving fetus.

Transvaginal ultrasound examination assisted the early diagnosis of these combined intrauterine and cervical ectopic pregnancies and provided the opportunity to attempt conservative management of the intrauterine pregnancy. With the advent of transvaginal ultrasonography an even earlier diagnosis of this condition is an increasing possibility. Ultrasound guided needle aspiration of the gestation sac or localized injection of methotrexate into the sac may then become feasible, with a reduced risk to the future reproductive potential for the woman.

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Fetal-pericardial effusion in association with congenital heart block and maternal systemic lupus erythematosus. Case report

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Case report

A 28-year-old woman who had had signs of intermittently severe systemic lupus erythematosus (SLE) for 2 years attended the antenatal clinic at eight weeks gestation in her second pregnancy. In the three years preceding this pregnancy she had had thrombocytopenic purpura, erythema nodosum and lymphocytic swelling of the salivary glands. Her first pregnancy at the age of 25 years was complicated by severe haemolytic anaemia and, later, by severe hypertension and resulted in a stillborn baby weighing 1380 g at 31 weeks. This outcome was attributed to placental infarction. Subsequently she had a Stevens-Johnson type illness with oculocutaneous manifestations. She had persistently high titres of antinuclear factor and anti-Ro (anti-SS-A) antibody, but insignificant levels of anticardiolipin antibody. Treatment had been with steroids and, at times, azathioprine.

In the current pregnancy prednisolone was increased from 5 to 10 mg/day and she was given low-dose aspirin (75 mg daily). At 18 weeks, ultrasonography showed a normal fetus with a normal heart rate. At 25 weeks a serious deterioration in the maternal condition occurred and she was admitted because of chest and loin pain, vomiting and pyrexia. She developed a small pleural effusion and had radiological and electrocardiographic evidence of myocarditis. The maternal anti-Ro antibody titre had risen from 1/1 to 1/4 but C-reactive protein levels were low. Ultrasound scan showed a normal size baby with normal cardiac anatomy and a normal atrial rate but a ventricular rate of about 56 beats/min and a small fetal pericardial effusion. Doppler studies showed increased impedance in the umbilical artery with reduced end-diastolic velocity. After an initial response to oral prednisolone (30 mg/day) she had a severe relapse and was given hydrocortisone intravenously, 1 g every 6 h for 24 h reducing slowly over the following week. The patient's condition improved rapidly and her remission was sustained with oral prednisolone (50 mg/day, reducing to 30 mg/day). Because it was suspected that the fetus had passively acquired the maternal autoimmune condition the prednisolone treatment was changed to oral dexamethasone (6 mg twice daily).

Perhaps in consequence of the high doses of steroids, glucose intolerance developed and insulin, increasing up to a total of 50 u/24 h, was needed for euglycaemia. Fetal growth was maintained but the fetal bradycardia and pericardial effusion persisted. The abnormal fetal umbilical arterial velocity pattern continued at the same level on Doppler recording.

At 34 weeks the C3 and total haem complement fell to 67 and 22% of normal pooled human sera respectively. We considered that there was early lupus reactivation and that both the maternal and fetal risks were increasing. An elective caesarean section was therefore undertaken. There was old meconium staining of the amniotic fluid. At birth the female baby, weighing 1840 g, had a profound bradycardia (60 beats/minute) but needed little resuscitation. The cord blood was anti-ENA (anti-Ro + anti-La) positive.

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Although the early neonatal period was complicated by mild idiopathic respiratory distress, the baby's cardiac output was satisfactory and cardiac pacing was not required. In view of the prolonged exposure *in utero* to high levels of glucocorticoids small doses of dexamethasone were given and then gradually withdrawn. No clinical features of adrenal insufficiency developed. After 10 days a small raised discoid erythematous lesion appeared on the baby's right leg. This resolved quickly with hydrocortisone cream. Electrocardiography confirmed the diagnosis of complete heart block and echocardiography reaffirmed the presence of a small pericardial effusion but again no cardiac malformation was identified. The effusion disappeared within a few weeks of birth. The child was discharged home at 6 weeks and remains well with a heart rate of 50–75/min without treatment.

The mother made a good postoperative recovery. The glucocorticosteroids were reduced slowly without problems and she reverted to prednisolone, 8 mg/day. Insulin requirement decreased in parallel and at 3 months postpartum glucose tolerance was normal without treatment The anti-Ro titre dropped to 1/1.

Discussion

We report this case primarily to record the finding of maternal anti-Ro antibodies and congenital heart block together with a small pericardial effusion. Although the association between maternal anti-Ro antibodies and congenital heart block has been adequately described (Esscher and Scott, 1979), we could only find one report in which there was also a fetal pericardial effusion (Hull *et al.* 1966). However, in the latter the fetus had a florid congenital pericarditis and the effusion was large. Doshi *et al.* (1980) reported a case of congenital pericarditis in connection with maternal lupus erythematosus which was associated with a severe fibrotic reaction but no effusion. In both these cases the fetal pericardial reaction, which was unsuspected before labour, was severe and both babies died. Although in our patient the nature of the fetal pericardial effusion was not clear we strongly suspect that the fluid represented an inflammatory exudate formed in response to mild pericarditis secondary to the transplacental passage of maternal auto-antibodies (Hull *et al.* 1966). The effusion in our patient was first found at the onset of a major episode of maternal pleuritis and myocarditis. Pleural and pericardial effusions frequently arise in patients with SLE when many are related to concurrent, opportunistic infection (Morrow and Isenberg, 1987). The low level of C-reactive protein suggested an inflammatory rather than infective aetiology in this case (Becker *et al.* 1980).

DeVore *et al.* (1982) have suggested that fetal pericardial effusion usually represents the first ultrasonographic manifestation of congenital cardiac failure. This does not seem to have been so in our patient even though a profound fetal bradycardia co-existed. A third possibility is that the effusion merely represents a common variation of normality occasionally found at high resolution ultrasonography (Jeanty *et al.* 1984) but we have not previously noted this finding.

The successful outcome of this pregnancy was dependent upon the prompt treatment of the deterioration in the maternal SLE with high dose parenteral hydrocortisone. Dexamethasone was given subsequently, in preference to prednisolone, as this leads to higher steroid concentrations in the fetal circulation (Blanford and Murphy, 1977) and should protect fetal cardiac function by having a suppressive effect on any fetal pericardial inflammatory reaction. Some clinicians have recommended aggressive immunosuppressive therapy for all pregnant women who have anti-Ro antibodies (Buyon *et al.* 1987; Barclay *et al.* 1987). Prospective studies of pregnant women with systemic lupus erythematosus and anti-Ro antibodies suggest that the risk of the fetus developing congenital heart block or other life-threatening manifestations of transplacental transfer of antibody is low (Lockshin *et al.* 1988). We believe the maternal complications of high dose corticosteroid therapy, which include diabetes mellitus as in our patient, and opportunistic infections preclude their use as prophylactic therapy for all pregnant women with a history of SLE.

In conclusion we suggest that the finding of a small fetal pericardial effusion in pregnancies complicated by maternal connective tissue disease and congenital heart block does not always indicate heart failure but should alert clinicians to the possible involvement of the fetal heart in the passively acquired allo-immune process. Prompt treatment with high-dose corticosteroids may prevent its progression and avert a life-threatening episode in early neonatal life.

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Ovarian dysgerminoma presenting with hypercalcaemia. Case report and review of the literature

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Case report

A previously healthy 17-year-old woman was referred to hospital because for 5 weeks she had had nausea, vomiting, lethargy and constipation. Her symptoms had persisted despite treatment with antiemetics and purgatives. A blood sample taken by her general practitioner revealed a serum calcium concentration of 3·9 mmol/l (serum albumin 35 g/l). Menstruation had occurred regularly since the age of 12 and had continued during her illness. She was menstruating one week earlier than expected when admitted to hospital for further investigation and treatment of hypercalcaemia.

On admission, she was dehydrated and clinically anaemic She had a normal female body with full development of secondary sexual characteristics. She was 165 m tall and weighed 65 kg. The blood pressure was 120/80 mmHg. The liver and spleen were not palpable. There was no lymphadenopathy. A large mid line mass could be felt arising from the pelvis, and lower abdominal swelling was clearly visible. The mass was firm, smooth and rounded and extended to 3 cm below the umbilicus. Bimanual examination did not clarify the origin of the mass.

Laboratory findings

The following results were obtained: haemoglobin 11·2 gm/dl; mean corpuscular volume 77 fl; white cell count 9·9 × 10^9/l; plasma glucose 5·0 mmol/l; bicarbonate 28 mmol/l; potassium 3·7 mEq/l; sodium 136 mEq/l; urea 12·1 mmol/l; creatinine 255 µmol/l; calcium 3·9 mmol/l; phosphate 0·92 mmol/l; albumin 41 g/l; total protein 86 g/l; total bilirubin 10 µmol/l; aspartate aminotransaminase 74 IU/l; alkaline phosphatase 323 IU/l; parathyroid hormone 0·2 µg/l (normal). The serum protein electrophoresis showed a diffuse increase in α and β globulins.

Ultrasound scan of the pelvis and lower abdomen showed a large solid mass of patchy texture measuring approximately 23 × 15 × 9 cm. The mass appeared to be continuous with the cervix and was, therefore, presumed by the radiologist to be a grossly enlarged uterus Neither ovary could be identified separately from the mass. The liver, spleen and kidneys were all normal. Computerized axial tomography of the pelvis and abdomen revealed a large soft tissue mass extending from just above the bladder to the level of the third lumbar vertebra in the lower abdomen (Fig. 1). The mass largely filled the peritoneal cavity and had a generally homogenous soft-tissue density with no cavitation or calcification.

Although the uterus and ovaries could not be clearly seen, the clinical diagnosis was of an ovarian tumour. There was no obvious abdominal lymphadenopathy and the liver appeared to be normal. A chest X-ray was normal.

After admission, she was rehydrated with intravenous fluids. This resulted in a fall in serum calcium to 3·44 mmol/l 24 h later, which remained at this level despite rehydration, and she continued to be symptomatic with persisting nausea. She was then treated with intravenous disodium etidronate, 450 mg infusions daily for 3 days followed by an oral maintenance dose of 1·2 gm daily for 2 weeks. The serum calcium was

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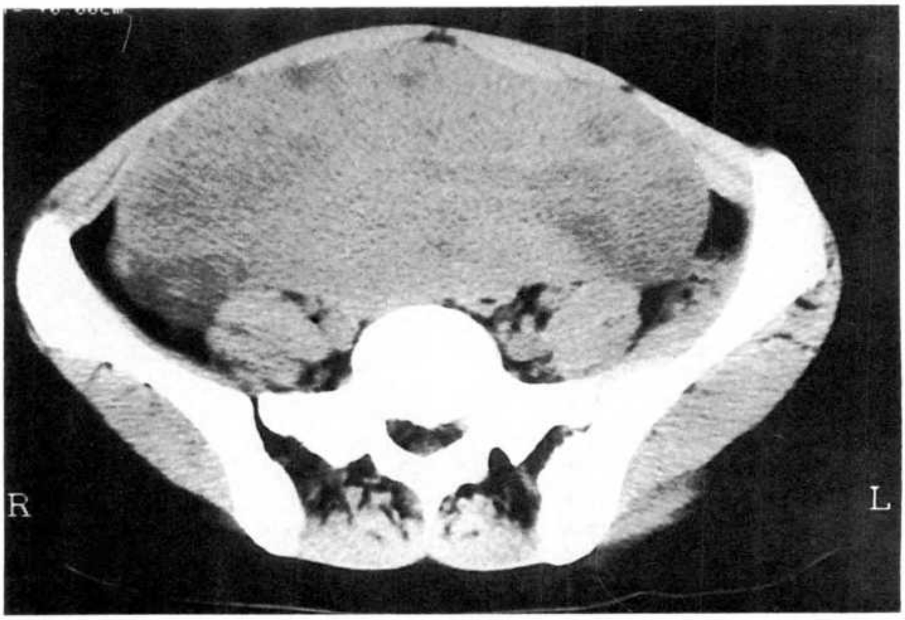

Fig. 1. CT scan of pelvis at the level of the third lumbar vertebra showing a large pelvic mass.

initially slow to respond to disodium etidronate and prednisolone, 50 mg twice daily for 2 days, was added to her therapy. Eight days after admission to hospital she was asymptomatic with a serum calcium of 2·86 mmol/l. The serum urea and creatinine returned to normal 12 days after presentation.

At surgery, a large, irregularly shaped, firm right ovarian mass was removed. The left ovary appeared congested but was otherwise normal. A small follicle was biopsied from the lower pole of the left ovary. No other intra-abdominal pathology was noted.

Treatment and progress

Following laparotomy she made an uncomplicated recovery. The serum calcium remained normal without further treatment. The raised levels of alkaline phosphatase and aspartate aminotransaminase both returned to the normal range after removal of the tumour. One month after surgery the CT scan of the abdomen was repeated and was normal. A lymphangiogram was also normal. Planned follow-up includes further CT scans at 3, 6 and 12 months.

Histopathology

The ovarian mass weighed 2357 g and had 7 cm of fallopian tube stretched over it. The external surfaces of the mass were smooth, bosselated and glistening whilst the cut surfaces were soft, predominantly solid with a few scattered cystic areas up to 1 cm in diameter.

On light microscopy the tumour showed typical features of a dysgerminoma. It was composed of cells with round nuclei, each with a prominent single nucleolus, and ample cytoplasm which varied from eosinophilic to clear. The cells were arranged mostly as solid islands separated by fine fibrous septa which were infiltrated by a mild inflammatory infiltrate composed of lymphocytes and plasma cells. Giant cells or syncytiotrophoblastic masses were not present in the multiple blocks examined. There was no positive staining for human chorionic gonadotrophin and alpha fetoprotein. The tumour infiltrated into but not through the ovarian capsule. The fallopian tube showed no histological abnormality. The biopsy from the left ovary showed cortex and stroma in which many primordial follicles and part of a cystic follicle were present.

Discussion

Dysgerminoma of the ovary is an uncommon gynaecological tumour representing 2% of all ovarian malignancies (Gallion *et al.* 1988); cure rates, even in the presence of metastases, are high (Asadourian *et al.* 1969). Management of stage 1 disease remains controversial with some recommending unilateral oophorectomy as the treatment of choice (Asadourian *et al.* 1988) whilst others advocate radiotherapy in addition to oophorectomy (Lucraft 1979).

Hypercalcaemia is the most common para-endocrine disorder associated with ovarian neoplasms and has been reported in cystadenocarcinomas (Josse *et al.* 1981, Plimpton & Gellhorn 1956), endometrioid, clear-cell (Stewart *et al.* 1982), small cell carcinoma (Dickersin *et al.* 1982), and undifferentiated carcinomas (Ferenczy *et al.* 1971). It has also rarely been described in association with dysgerminoma (Breidahl & Richie 1962; Nelken *et al.* 1978; Stewart *et al.* 1980) (Table 1).

The cause of hypercalcaemia of malignant tumours is often obscure. A number of different mechanisms have been described including osteolytic metastases (Jessiman *et al.* 1963), ectopic parathyroid hormone production (Buckle *et al.* 1974), elevated calcitriol levels (Breslau *et al.* 1984), and tumour secretion of humoral calcaemic factor (Powell *et al.* 1973).

Most patients with ovarian neoplasms complicated by hypercalcaemia have symptoms attributable to hypercalcaemia (Jessiman *et al.* 1963). Hypercalcaemia does not result in early diagnosis, being associated with a large tumour mass (Stewart *et al.* 1980) as seen in all four patients with dysgerminoma detailed in Table 1. This may be explained by limited biological activity of humoral factors, inefficient synthesis or secretion of humoral factors or normal homeostatic mechanisms keeping the serum calcium in the normal range until overwhelmed at a late stage when the tumour mass is large (Steward *et al.* 1980).

Impairment of renal function with severe hypercalcaemia is frequently seen, as in our patient, and usually returns to normal once rehydration and normocalcaemia have been established

Germinoma cells are known to posssess mixed enzymes of alkaline phosphatase, consisting mainly of the liver and bone isoenzymes with a small amount of the D-variant of the placental type on the cell surface (Koide *et al.* 1988). In the apparent absence of bone or liver metastases, and with the return of serum alkaline phosphatase to normal after surgery, the most likely origin for the raised alkaline phosphatase in our patient was from the dysgerminoma itself. The mildly elevated asparatate aminotransaminase, on presentation, is harder to explain, as this ubiquitous enzyme has many possible origins.

Both lactate dehydrogenase (Schwartz & Morris 1988) and alkaline phosphatase (Dgani *et al.* 1988) have been reported as possible tumour markers useful for the diagnosis and follow-up of ovarian dysgerminoma.

In conclusion, we have described the rare association of dysgerminoma and hypercalcaemia. Our patient presented with symptoms of hypercalcaemia and was found to have a large dysgerminoma confined to one ovary. The marked hypercalcaemia observed on presentation did not recur after surgery, suggesting

Table 1. Previous reports of dysgerminoma of the ovary complicated by hypercalcaemia

Reference	Age (years)	Stage	Serum calcium at presentation	Extent of disease	Outcome
Breidahl and Ritchie (1962)	40 nulliparous	IV	17·8 mg/dl (4·45 mmol/l)	Right ovarian mass, 10 × 6 × 6 cm, multiple tumour metastases in thorax, abdomen and pelvis	Death, shortly after diagnostic thoracotomy
Nelken *et al.* (1978)	10	I	12 3 mg/dl (3·07 mmol/l)	Left ovarian mass 20 × 13 × 11 cm, weight 1230 g, no metastases	Patient alive and well with no evidence of tumour recurrence at 5 year follow-up
Stewart *et al.* (1982)	15	III	Unknown	Left ovarian mass 19 × 11 × 17 cm, weight 860 g, para-aortic lymph node	Unknown
Present study	17 nulliparous	I	3·9 mmol/l	Right ovarian mass 28 × 17 × 11 cm, weight 2357 g, no metastases	Patient alive and well with no evidence of tumour recurrence at 3 month follow-up

humorally mediated hypercalcaemia. Treatment was limited to unilateral salpingo-oophorectomy with preservation of reproductive potential.

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Tamoxifen and endometriosis. Case report

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Case report

A 44-year-old woman had received 20 mg of tamoxifen daily for three years, for the treatment of breast carcinoma. She attended the gynaecological clinic because she had had intermenstrual and postcoital bleeding for six months and amenorrhoea for four months. She had a hysterectomy and bilateral salpingo-oophorectomy for the relief of her symptoms. Examination of the operation specimen showed severe simple endometrial hyperplasia and simple hyperplasia was also present in the endometriotic foci in the ovary (Fig. 1). There was no evidence of atypical hyperplasia or carcinoma in either the endometrium or the endometriotic foci and no metastatic breast carcinoma was detected in the tissues examined.

Discussion

Tamoxifen is a nonsteroidal synthetic oestrogen usually regarded as an antioestrogen. Its behaviour is, however, more typical of a partial agonist (MacNab *et al.* 1984), exhibiting oestrogen agonistic or antagonistic effects depending upon the relative concentrations of oestrogen and tamoxifen. In experimental conditions the drug has an antagonistic effect when endogenous oestrogen levels are high and an agonistic effect when oestrogen levels are low. Its use, therefore, particularly in the premenopausal patient, usually results in a reduction in the effect of endogenous oestrogen and it is widely used, for this purpose, in the treatment of oestrogen receptor-rich breast carcinoma. It has been recognized, however (Killackey *et al.* 1985; Gottardis *et al.* 1988; Fornander *et al.* 1989; Buckley and Fox, 1989), that, in certain circumstances, its potentiation of an oestrogenic effect may result in the development of endometrial hyperplasia or stimulation of endometrial carcinoma. The stimulatory effect of oestrogens on endometriotic foci is sometimes overlooked although the sensitivity of endometriosis to hormones is used to advantage in its treatment.

Fornander *et al.* (1989) reported that patients receiving tamoxifen for the treatment of early breast carcinoma were not, in general, more likely to develop a second carcinoma than those treated by other means, but among the tumours that developed, there was an excess of endometrial carcinomas: such tumours have been reported in both premenopausal and postmenopausal women (Killackey *et al.* 1985). It has also been shown, experimentally, that whilst tamoxifen has an inhibitory effect on breast carcinoma transplanted into nude mice, it may in similar circumstances have a stimulatory effect on endometrial carcinoma (Gottardis *et al.* 1988; Jordan, 1988). There is also evidence that postmenopausal patients treated with tamoxifen have an increased risk of endometrial and endocervical polyps and that the endometrium is more likely to be hyperplastic than in controls (Neven *et al.* 1989).

It has been suggested that tamoxifen might be an acceptable form of treatment for endometriosis in women wishing to conceive, as during its use ovulation is not regularly inhibited (Haber and Behelak, 1987). However, there is also evidence that endometriosis may be stimulated or develop when tamoxifen is used (Ford *et al.* 1988).

There have been, to the best of my knowledge, no previous reports of hyperplasia of endometriotic foci during tamoxifen therapy. The implications of this finding are clear. Many women undergo simple hysterectomy for menorrhagia with conservation of the ovaries. Had this procedure been chosen in this patient she

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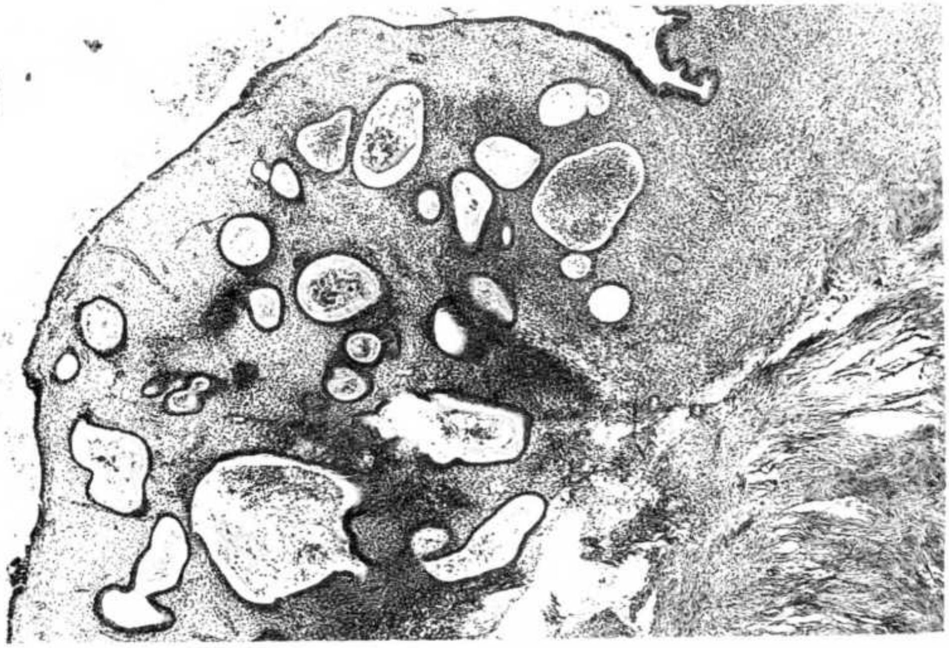

Fig. 1. A nodule of endometriotic tissue, with the features of simple (cystic glandular) hyperplasia, in the lining of an ovarian endometriotic cyst (H&E × 37).

would have been at risk of pain and discomfort from the active endometriotic foci and at risk, albeit a low one, of developing adenocarcinoma in the foci of endometriosis in the ovary.

The possibility of the induction of malignant change, not just in the endometrium, but also in endometriotic foci should not be overlooked when treating patients with tamoxifen. The suggestion that a progestogen might be given to prevent the carcinogenic effect of the tamoxifen on the endometrium and endometriotic foci is not recommended as the progestogen may reverse the antitumour effect of the drug (Jordan, 1989).

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Small cell carcinoma of the cervix with inappropriate antidiuretic hormone secretion. Case report

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Case report

A 69-year-old woman was admitted to the department of Internal Medicine in May, 1988, because she had had nausea and vomiting for 10 days. During this period she drank only water and tea. A few days before admission she became lethargic and developed headache. There were no other complaints. She did not use any medication and her previous health had been good. Her menopause had occurred when she was 53. She smoked about 20 cigarettes a day. On admission the patient appeared a little confused. Blood pressure was 175/70 mmHg (6 months previous 130/80 mmHg), pulse rate 88 beats/min, juxtavenous pressure was normal, temperature 36·6°C Except for a little ankle oedema there were no abnormalities on physical examination. No gynaecological abnormalities were found on vaginal examination. Neurological examination was normal.

The following laboratory data were obtained: ESR 31 mm in the first hour, haemoglobin 13·0 g/dl, haematocrit 0·39 l/l, WBC 4·8 × 10^9/l, with a normal differentiation, platelets 198 × 10^9/l, serum sodium 112 mmol/l, potassium 3·6 mmol/l, chloride 87 mmol/l, bicarbonate 21·2 mmol/l, plasma osmolality 231 mosmol/kg, serum creatinine 55 μmol/l, plasma glucose 4·3 mmol/l, urea 2·5 mmol/l, normal values for alkaline phosphatase, ASAT and ALAT.

Urine osmolality was 495 mosmol/kg, urine sodium 39 mmol/l. Levels of thyroid hormones, plasma cortisol and aldosterone were all normal. There were increased concentrations of atrial natriuretic peptide: 80 ng/l (normal range 9–68 ng/l) and antidiuretic hormone: 2·9 ng/l (normal range 0·2–1·5 ng/l).

An X-ray of the chest and a CT-scan of the brain were normal but a CT-scan of chest and abdomen revealed small mediastinal and large retroperitoneal lymph nodes; the lung fields were clear.

Cytological examination of the retroperitoneal lymph nodes revealed an undifferentiated small cell carcinoma. At gynaecological examination a friable oedematous cervix was seen without evident tumour growth. The cervical smear was suspect for carcinoma and colposcopic biopsies were taken from suspicious areas. Histological examination revealed the same undifferentiated small cell carcinoma. The diagnosis of a cervical carcinoma stage IV was made.

We treated our patient with fluid restriction and sodium chlorid capsules, after which the plasma sodium rose and stabilized at 133 mmol/l with a plasma osmolality of 275 mosmol/kg. She lost 6·7 kg in weight and her blood pressure fell to 125/75 mmHg. She refused our offer of chemotherapy and returned home on July 8. In August 1988 she complained of dyspnoea at rest and a nonproductive cough, and lymphangitis carcinomatosa of the lungs was diagnosed. Eventually she accepted chemotherapy with cyclophosphamide 800 mg/m^2, vincristine 1·4 mg/m^2 and methotrexate 40 mg/m^2 every 3 weeks. After two courses dyspnoea and cough had disappeared and an X-ray of the chest showed complete disappearance of the

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abnormalities. She refused further cytostatic treatment. In December 1988 a clinical diagnosis of tumour involvement of the sacral plexus was made, but she refused further chemotherapy. Her clinical condition deteriorated rapidly and she died in January 1989.

Discussion

Hyponatraemia can be a component of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The excess of ADH results in water retention, which eventually leads to hyponatraemia. Ever since the first clinical description (Schwartz *et al.* 1957), the syndrome has been associated with a variety of tumours, especially small cell carcinomas of the lung (De Vitra Jr *et al.* 1985). To our knowledge the association of SIADH with small cell carcinoma of the cervix has not been described before.

Hyponatraemia and hypo-osmolality together with a high sodium urine concentration and a high urine osmolality, in the presence of normal cardiac, kidney and liver function, favour the diagnosis of the SIADH (Schwartz *et al.* 1957). Our patient had no signs of adrenal or thyroid insufficiency.

Although usually in this syndrome inappropriately elevated serum ADH levels are reported, in about 10% of the patients the serum ADH levels are low or normal (Zerbe *et al.* 1980). Perhaps in those patients another antidiuretic substance is produced, not reactive with the monoclonal antibody used in the ADH assay.

The slightly elevated level of atrial natriuretic peptide found on admission has been described in patients with SIADH (Cogan *et al.* 1986; Donckier *et al.* 1986); volume expansion is likely to be the stimulus for the production of atrial natriuretic peptide, which is, at least partially, responsible for the natriuresis in SIADH.

A diagnosis of cervical carcinoma was made. There is a theoretical possibility of a primary, occult bronchial carcinoma, but the presence of the cervical lesion and extensive iliac and para-aortic lymph node metastases makes this diagnosis unlikely.

Also, CT scanning of the thorax is a very sensitive method for detecting pulmonary tumours. In two recent studies, abnormalities were seen in the lung parenchyma or bronchi in 96–98% of primary pulmonary malignancies (Henschke *et al.* 1987; Mayr *et al.* 1987).

About 4% of all cervical carcinomas show a small cell carcinoma pattern (Van Nagell *et al.* 1977). These are usually divided into small cell non-keratinizing squamous carcinoma, reserve cell carcinoma, cervical carcinoid and the small cell undifferentiated or oat cell carcinoma (Groben *et al.* 1985). Cushing's syndrome as a consequence of ectopic ACTH production in a small cell undifferentiated cervical carcinoma (which showed neurosecretory granules on electron microscopy) was described some years ago (Jones *et al.* 1976). In our patient an oat cell cervical carcinoma was responsible for a SIADH.

We believe that our case provides evidence that the small cell undifferentiated cervical carcinoma can be added to the list of tumours which can cause the syndrome of inappropriate ADH secretion.

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Granulosa cell tumour of the ovary producing both oestrogen and progesterone. Case report

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Case report

A 36-year-old woman was referred to a gynaecologist in 1985 because of intermenstrual bleeding and irregular cycles between 28 and 42 days. An endometrial sample obtained by Vabra aspiration revealed slightly hyperplastic changes in the glands. Her symptoms disappeared afterwards and no further treatment was considered necessary.

Three years later in 1988, she developed amenorrhoea of 7 months duration; this was associated with breast tenderness, heartburn and gradual abdominal distension. Subsequent investigation by ultrasonography detected a large multiloculated cystic mass arising from the pelvis, measuring 22 cm in diameter, confirmed by laparotomy to be a cystic tumour of the left ovary. Left oophorectomy, together with biopsies of the omentum and right ovary, were performed. Histologically the tumour was a granulosa cell tumour with classical Call-Exner bodies. A mitotic count of 15 per 10 high power field was noted, but there was no neoplastic involvement of the right ovary or the omentum. During the subsequent follow-up, she had three regular monthly periods but thereafter became amenorrhoeic again. There was persistent elevation of serum oestradiol (Fig. 1), suggesting that the tumour had recurred. As a result, a second laparotomy was performed, and she had a total abdominal hysterectomy and right salpingo-oophorectomy. The uterus was enlarged, approximately equivalent in size to a 14 week pregnancy. There was no evidence of pelvic or intra-abdominal metastasis of the tumour.

Histologically, there was no evidence of ovarian neoplasia, but surprisingly the endometrium had marked pseudodecidual changes in the stroma associated with inactive endometrial glands, suggestive of progestogen influence. However, the patient denied taking any hormonal medication for three months before the laparotomy. This prompted us to measure progesterone in plasma samples obtained before the second laparotomy, this was found to be grossly elevated (Fig. 1). Unfortunately, plasma oestradiol and progesterone levels did not fall after the operation. Further investigation by computerized axial tomography revealed a 5 cm mass in the left para-aortic region, consistent with a lymph node metastasis. Shortly afterwards, she had a third laparotomy and a solitary para-aortic tumour was removed which was confirmed histologically to be metastatic granulosa cell tumour. Steroid receptor concentrations in the metastatic tumour were 9·6 fmol/mg protein for oestradiol, 1·2 fmol/mg protein for progesterone and 2·4 fmol/mg protein for androgen.

Post-operatively, she had a course of whole abdomen radiotherapy. Initially this used 38 cm by 23 cm parallel opposed fields with suitable shielding, 6 MV photons and a rising input. She tolerated this badly and it was quickly modified to a 'spade' pattern. This arrangement too

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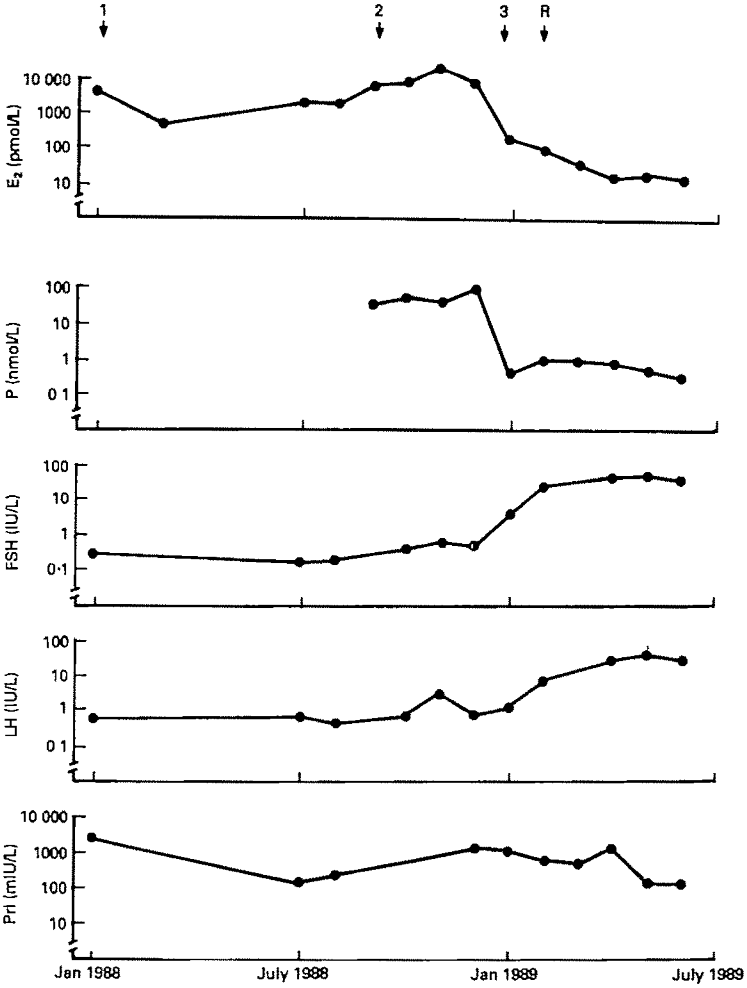

Fig. 1. Plasma concentrations of oestradiol (E_2), progesterone (P), follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (Prl) in a patient with granulosa cell tumour producing large amounts of both oestrogen and progesterone. 1, first laparotomy, 2, second laparotomy; 3, third laparotomy; R, radiotherapy.

proved unpleasant with severe vomiting, diarrhoea and abdominal pain. She then received pelvic radiotherapy and a limited para-aortic cylinder given by 10 MV rotational therapy.

In all she received a cumulative dose of 4900 cGy to the para-aortic area, and 4400 cGy to the pelvis with a maximum dose of 3100 cGy to the spinal cord and 2250 cGy to half of the left kidney, all in 55 days.

Although the treatment underwent several modifications, and was more extended in time than we had wished because of her severe nausea and vomiting, the tumour showed a satisfactory response and no adjustment was made to the radiotherapy dose for the gaps in treatment.

Endocrinology

Plasma concentrations of oestradiol, progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin throughout the period of study are summarized in Fig. 1. In addition, plasma sex hormone binding globulin was much increased at 295 nmol/l (reference range 50–80 nmol/l) before the third laparotomy, after which the concentration fell to

Table 1. Endometrial histology in granulosa cell tumour.

Authors	Total number of cases	Endometrial histology					
		Normal*	Proliferative (unusual)	Polyp	Hyperplasia	Carcinoma	Sarcoma
Pankratz *et al.* (1978)	24	4	0	0	16	3	1
Fox *et al* (1975)	59	14	6	4	29	6	0
Stenwig *et al.* (1979)	64	7	13	0	42	2	0

*None mentioned to have secretory changes.

100 nmol/l. Other endocrinological investigations before the third laparotomy included plasma testosterone, androstenedione and cortisol concentrations which were normal, urinary excretions rates of 17- hydroxyprogesterone and progesterone metabolites which were high, and urinary metabolites of 21- deoxycortisol which were not detected.

Discussion

Clinically, granulosa cell tumour is characterized by its ability to produce oestradiol (E_2) and this serves as a useful tumour marker. The production of progesterone by granulosa cell tumour is extremely rare and has only been reported once before by Lomas *et al.* (1977). There is further indirect published histological evidence to suggest that progesterone production by granulosa cell tumour must be rare because endometrial histology often shows the features of excessive oestrogen stimulation such as hyperplasia. In addition endometrial carcinoma occurs in about 5–10% of women with granulosa cell tumour (Table 1). The histological findings of the endometrium were well described in three series which are summarized in Table 1. Of particular interest is that none of these investigators, including Evans *et al.* (1979) who reviewed a further 119 cases of granulosa cell tumour, reported on the presence of any (unusual) progestogenic effect in the endometrium.

In our patient, both oestradiol and progesterone were produced in significant amounts by the tumour. The absolute plasma progesterone concentration was 2–4 times higher than that of oestradiol, suggesting that more progesterone was produced than oestradiol. This is in keeping with the findings of marked progesterone effects in

The ability of granulosa cells to produce progesterone is not surprising because this is normally produced by luteinized granulosa cells in the corpus luteum. What is surprising, perhaps, is that progesterone production by granulosa cell tumour has so rarely been reported. The reason for this is unclear, but one possibility is that these cells do not usually possess LH receptors and so rarely become luteinized.

On the other hand, the presence of both oestrogen and progesterone receptors in the tumour in our patient suggests that oestrogen and progesterone produced by the tumour may have had an autocrine stimulatory effect on growth of the neoplasm. The presence of androgen receptor protein is unexplained.

In the first report of granulosa cell tumour producing progesterone (Lomas *et al.* 1977) the tumour produced only a small amount of oestradiol. In contrast, in the present second report, both progesterone and oestradiol were produced in excessive amount. The large amount of oestradiol produced by the tumour helps to explain many of the clinical and endocrinological changes observed. amenorrhoea, breast tenderness, nausea, enlarged uterus, elevated plasma prolactin, grossly elevated sex hormone binding globulin, and low levels of plasma gonadotrophins.

Although granulosa cell tumour of the ovary has not previously been reported to produce high levels of both oestradiol and progesterone, it is of interest that (i) granulosa cell tumour of the ovary is occasionally associated with virilization (Sternberg & Dhurandhar, 1977; Norris & Taylor, 1969); and (ii) lipid cell tumour of the ovary has been reported to produce both oestrogens and progesterone, although the predominant steroids produced are androgens

This report describes the first case of granulosa cell tumour producing excessive amounts of both oestradiol and progesterone. Although the clinical significance of progesterone production by granulosa cell tumour is still uncertain, plasma progesterone concentration should, in the future, be measured in women with granulosa cell tumour so that the prevalence and clinical significance of such a finding can be assessed in due course.

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SHORT COMMUNICATIONS

Monitoring the fetus with a pulse oximeter during a caesarean section

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It is possible to monitor continuously the fetus during labour with a pulse oximeter (Johnson & Johnson, 1989), and in this study we attempted to monitor fetal oxygen saturation with a pulse oximeter during caesarean section.

Subjects and methods

Subjects undergoing caesarean section were positioned with 15° of left lateral tilt and a reflectance pulse oximetry probe was passed through the cervix to rest between the presenting fetal part and the side wall of the lower uterine segment. In women delivered by elective section the probe was placed extra-amniotically. It was constructed from the light-emitting diodes and photo-detector from a Criticare Multi-site Sensor Probe which was stripped of the rubber surroundings and encased in a single silicone mould. Continuous fetal arteriolar scalp oxygen saturation (Criticare, Milwaukee, USA 502 Pulse Oximeter), intrauterine pressure, fetal heart rate, infra-red plethysmograph (pulsatile component of detected light; Johnson *et al.* 1989) and all stages of the caesarean section were continually recorded. Only if the fetal heart rate was within 110–170 beats/min were the values accepted. The average oxygen saturation for each stage of the operation was calculated by microcomputer based on measurements taken every 5 s. The change in oxygen saturation for each operative stage was calculated from the mean saturation for each stage of the operation minus the overall mean oxygen saturation for that baby

Each operation was divided into five stages: stage 1, from placement of the probe to incising the skin; stage 2, from the first skin incision to the first incision in the rectus sheath; stage 3, from opening the sheath to exposing the uterus; stage 4, from exposing the uterus to incising the uterus; stage 5, from incising the uterus to delivering the fetus. Once the uterus had been incised and the fetus exposed, recordings were maintained for 2 min.

Results

The plethysmograph was invariably distorted as the uterus was manipulated and in 12 women the reading was temporarily lost as the vesical peritoneum was breached. In four women, recording after the uterine incision was impossible because bleeding from the uterine incision forced the surgeon to expedite delivery and five other recordings were incomplete because of equipment failure. We failed to obtain any satisfactory reading in several other cases because of probe dislodgement, loss of contact or because the probe could not be passed through the cervix.

Intra-operative oxygen saturation was measured successfully on 24 fetuses from 14 women undergoing elective lower segment caesarean section and 10 women undergoing emergency lower segment caesarean section because of cephalopelvic disproportion. Seven women received general anaesthesia and were pre-oxygenated for approximately 5 min and 17 women had epidural analgesia and did not receive supplementary analgesia or oxygen until the baby was born. All babies who were successfully monitored with the uterus open for at least 2 min were born in good condition (Apgar score >8 at 1 min; mean umbilical vein blood pH 7·35 (SD 0·58, range 7·43–7·23) and the calculated oxygen saturation was 67% (SD 16%, range 47–85%). The umbilical artery blood pH at birth was 7·26 (SD 0·03, range 7·0–7·29). Meconium was not observed in any case.

Fetal oxygen content does not appear to increase or decrease substantially during any part of the operation. A slight but statistically insignificant rise in fetal oxygen saturation (mean 0·5% SEM 1·5%) occurred after the skin incision. No marked change in oxygen saturation occurred after incision of the uterus (average decrease at delivery = 0·7%; SEM 2·7%; ß = 0·8; paired *t*-test); (Fig. 1).

Discussion

It is possible to monitor the fetus through intact membranes during a caesarean section. Whilst our observation may provide some reassurance for those who take care and time in delivering the fetus, it must be emphasized that all our cases involved low-risk fetuses who had a normal cardiotocography, and it is possible that the findings may be different in hypoxic babies with no placental reserve. The slight rise in oxygen saturation (0·5%) after the skin incision could be due to maternal hyperventilation but it could equally have occurred by chance. Although there are limitations to pulse oximetry and fetal oximetry is still being pioneered, we support the findings by Crawford & Davies (1982) that the time from incision to delivery is not correlated with fetal acid-base status.

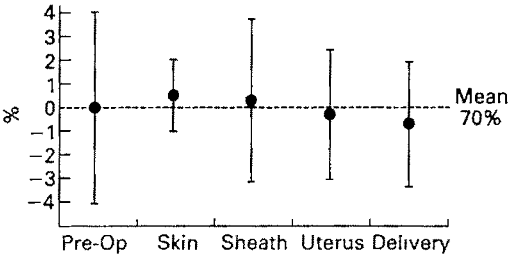

Fig. 1. The change in fetal scalp arterial oxygen saturation occurring during a caesarean section (mean SaO_2 ± SEM).

The signal strength and character was judged by analysing the plethysmograph. Movement interference was observed universally as the uterus was manipulated and although the oximetry reading continued to be recorded, readings during this period must be discarded.

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Prognosis of pregnancies conceived by donor insemination with respect to the late follicular phase luteinizing hormone levels

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It has been suggested that exposure to abnormally elevated level of luteinizing hor-

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Table 1. Luteinizing hormone (LH) levels before the LH surge in women conceiving with donor insemination related to outcome.

Days before LH surge	Pregnancy outcome	*n*	LH level (mIU/ml) mean	(SD)	Mean difference (95% CI)
3	Miscarriage	11	10·2	(4·0)	3·5 (−0·6 to 7·6)
	Continuing	51	13·7	(6·5)	
2	Miscarriage	20	14·5	(6·7)	1·0 (−2·2 to 4·2)
	Continuing	80	15·5	(6·5)	

mone (LH) during late follicular phase during the conceptional cycle may contribute to early pregnancy loss after in vitro fertilization (Howles *et al.* 1986) and after ovulation induction in women with polycystic ovarian syndrome (Abdulwahid *et al.* 1985). To test the hypothesis that this may also apply to spontaneous cycles, we carried out a retrospective analysis of 100 conceptions following donor insemination (DI).

Subjects and methods

Between January 1986 and December 1987, 150 conceptions resulted from the use of donor insemination at the Insemination Service, Prince Henry's Hospital, Melbourne. The routine for donor insemination has previously been described in detail (Kovacs *et al.* 1988). The only modification that has taken place since that report is of LH estimation using double antibody with human serum calibration (Diagnostic Products Corporation L.A. California). All women attended daily when it was estimated that ovulation may be taking place, and early morning blood samples were taken. A rapid LH assay was then performed, and the circulating levels of LH were assayed quantitatively.

A retrospective analysis compared LH levels between women with ongoing pregnancies and those who had first-trimester miscarriages. Levels were available for 100 women 2 days before, and for 62 women 3 days before the LH surge, defined as a significant rise in LH over previous basal levels. The levels of LH were compared by two-way analysis of variance, considering the effects of days and outcome of pregnancy.

Results

Of the 100 women for whom results were available 2 days before the LH peak 20 miscarried, and of the 62 for whom results were available 3 days before the peak 11 miscarried.

Table 1 gives the mean LH levels, these were slightly lower in those with miscarriages than in those with ongoing pregnancies. The two-way analysis of variance showed there was a statistically significant difference in the LH levels between the 2 days but no significant difference ($P=0{\cdot}3$) between LH levels for women having miscarriages and those with an ongoing pregnancy.

Discussion

It has been suggested that women with raised LH levels during the follicular phase miscarry more often after IVF and ovulation induction. The postulated mechanism is that LH may alter the hormonal environment within the follicle, and so cause abnormal development of oocytes (Stanger & Yovich, 1985). In this study of conceptional cycles during donor insemination, there was no associate between late follicular LH levels and subsequent pregnancy outcome. Our study therefore supports the finding of Thomas *et al.* (1989) who found that raised serum LH levels did not predict the clinical outcome of 331 conceptions following IVF.

We therefore conclude that the hypothesis that elevated follicular levels of LH are associated with a poorer prognosis is unproven

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Endometrial resection when hysterectomy is undesirable, dangerous or impossible

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Transcervical resection of the endometrium using a standard urological resectoscope, has recently been described as a treatment for menorrhagia when medical management proves unsatisfactory but the patient does not want to undergo hysterectomy (Magos *et al.*, 1989a). By avoiding major surgery, the procedure has the advantage of much shorter hospitalization and recovery time. Endometrial resection can even be performed under light sedation and local anaesthesia on an outpatient basis or on women unfit for general anaesthesia (Magos *et al.* 1989b). These considerations led us to assess the technique in four women with abnormal menstruation whose pre-existing medical conditions meant that hysterectomy was either technically or medically contra-indicated.

Patients, methods and results

Details of the four patients are shown in Table 1. They all suffered from heavy periods which were painful in two (nos. 2 and 3) and frequent in one (no. 1). Pelvic examination was normal in all four women, and all of them had tried conservative therapy in the past. Danazol, norethisterone or buserelin was prescribed preoperatively to prepare the endometrium for surgery.

The technique of transcervical resection of the endometrium was as described previously, using sterile 1.5% glycine solution to distend and irrigate the uterine cavity (Magos *et al.* 1989a). Two patients opted to have the procedure without general anaesthesia under a combination of sedation (intravenous midazolam), systemic analgesia (intravenous fentanyl) and paracervical, intracervical and intrauterine local anaesthesia (1% lignocaine with 1:200 000 adrenaline). The medical condition of the woman with mitral valve disease necessitated antibiotic prophylaxis, additional to the usual pre-operative regimen of intravenous cefuroxime and metronidazole. Surgery was completed without difficulty in all women and pre- and post-operative blood tests confirmed the absence of significant disturbance of biochemical or haematological indices.

There were no post-operative complications. The mean hospital stay was 1·4 days, excluding the patient who required a prolonged stay to stabilize anticoagulant therapy. Post-operative uterine bleeding lasted between 2 and 10 days. During follow-up for up to one year, three of the four patients have remained amenorrhoeic and

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Table 1. Patient and operative details

Patient	Age (years)	Parity	Medical condition	Procedure	Hospital stay	Follow-up (months)	Menstrual result
1	44	3+0	Severe multiple sclerosis, sacral neurectomy	Total TCRE under GA	3 days	12	Two episodes of spotting
2.	27	0+0	Spina bifida, paraplegia, ileal conduit	Total TCRE under LA	24 h	8	Amenorrhoea
3	35	0+0	Five previous laparotomies dense pelvic adhesions, attempted hysterectomy abandoned	Total TCRE under LA	12 h	7	Amenorrhoea
4	35	0+0	Mitral valve replacement for rheumatic heart disease, atrial fibrillation, treated with digoxin and warfarin	Total TCRE under GA	15 days	6	Amenorrhoea

TCRE, Transcervical resection of the endometrium.
GA, General anaesthesia.
LA, Local anaesthesia.

pain-free; the fourth has had two short, painless episodes of spotting. Out-patient hysteroscopy was performed 3 months after resection and showed varying degrees of intrauterine fibrosis and obliteration of the cavity. All the women were completely satisfied with the results of the treatment.

Discussion

Hysteroscopic endometrial destruction by surgical diathermy was first described by DeCherney & Polan (1983) as an emergency treatment for intractable and life-threatening uterine bleeding in women who were suffering from conditions such as leukaemia and aplastic anaemia, or who were unfit for conventional surgery. The authors noted in this, and a follow-up study (DeCherney *et al.* 1987), that surgery was followed by amenorrhoea or slight spotting; only one of their 19 surviving patients required a repeat procedure. Our experience shows that our technique of endometrial resection is also suitable for women who are not good candidates for long-term drug treatment or hysterectomy.

Prolonged hormonal manipulation may be inappropriate when there is no requirement to preserve fertility but hysterectomy may seem unnecessarily drastic. On the other hand, hysterectomy may be considered too hazardous because of potential risks associated with, for example, dense pelvic adhesions, an ileal conduit, lower limb paralysis, or long-term anticoagulant therapy, as in our patients. Under these circumstances, transcervical resection of the endometrium appears to be a safe, effective and readily acceptable solution to menstrual problems. Although the operative risks of extensive intrauterine surgery are still being identified (Magos *et al.* 1990; Baumann *et al.* 1990), they appear to be considerably less than with hysterectomy (Dicker *et al.* 1982). Effective treatment for amenorrhoea can now be offered to women for whom hysterectomy is regarded as undesirable, dangerous or even impossible.

Acknowledgments

We are grateful to Rimmer Brothers, London, UK, and Karl Storz GmbH, Tuttlingen, West Germany for loan of the resectoscope, and our colleagues who referred the patients. GML was supported by a grant from Medical Research Fund, and RB by Locally Organized Research.

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CORRESPONDENCE

Do raised serum luteinizing hormone levels during stimulation for in-vitro fertilization predict outcome?

Dear Sir,

I wish to reply to the article by Thomas *et al.* (*Br J Obstet Gynaecol* (1989) **96**, 1328–1332) on the value of serum LH concentrations for predicting IVF outcome Whilst the statistical analysis is very valid for their series of patients, I feel that the authors have seriously misinterpreted the previously published work by Howles *et al.* (1986). There are a number of points I would like to clarify, the most important are discussed below.

These initial results (Howles *et al.* 1986) were published later in a more complete form (Howles *et al.* 1987*a*). A larger group of patients recruited prospectively (Howles *et al.* 1987*b*) were subjected to univariate and multivariate analysis of variance, which confirmed these initial observations

With regard to whether the LH detection system used was valid, the results were obtained using a double monoclonal antibody sandwich assay which only identifies *whole* LH molecules. The biological specificity of this assay was clearly reflected in its ability to predict accurately the subtle fluctuations in LH that were associated with an LH surge, leading to the successful recovery of healthy mature oocytes.

Finally, as the authors stated, the quoted article by Howles *et al.* (1986) did not include patients undergoing an endogenous LH surge. This is a most important point which clearly differentiates the patient populations studied.

Results from a number of workers (Messinis *et al* 1985, Glasier *et al.* 1988, Howles and Macnamee 1989) have shown that if an endogenous LH surge occurs after clomiphene citrate hMG therapy, it is grossly attenuated and hence difficult to detect Nevertheless, if intensive LH monitoring is carried out and the appropriate action is taken, the pregnancy rate in patients who surged was as good as that in patients who were given hCG to time oocyte recovery, (Macnamee *et al.* 1987; Caspar *et al* 1988). In summary, therefore, I would agree with Thomas *et al.* that raised LH levels associated with a properly identified endogenous surge are not deleterious to pregnancy outcome.

In contrast, the studies of Howles *et al.* (1986; 1987*a,b*) were concerned with raised but *tonic* levels of LH (not sufficient to elicit follicular rupture). This phenomenon was associated with a reduced rate of pregnancy, or if pregnancy occurred, an increased likelihood of miscarriage.

More recently published work on other groups of infertile and fertile women have lent credence to this hypothesis. Homburg *et al.* (1988) reported that in PCO patients, LH levels at the time of maximum follicular development were significantly lower in those who conceived compared to those who did not Similarly, Johnson & Pearce (1990) found an association between the ratio of LH to maximum follicular diameter and the occurrence of miscarriage in PCO patients with a history of recurrent miscarriage. Watson *et al.* (1989) have demonstrated that 48% of their patients who suffered from recurrent miscarriage had follicular phase abnormalities of LH secretion. Even more intriguing are the results of a field study in normal women with spontaneous menstrual cycles (Regan *et al.* 1989) Here, follicular phase LH concentrations were related to rates of fertility and miscarriage. Again the conception rate was higher (80% *vs* 61%) in those patients who had normal LH levels (<10IU/l) compared to those with high levels (>10IU/l) during the follicular phase

In conclusion, there are a growing number of reports which support the hypothesis that follicular phase LH secretion is associated with reproductive outcome.

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Author's reply

Dear Sir,

Thank you for the opportunity to reply to Dr Howles' letter.

I think we all agree that the issue of serum LH concentrations and pregnancy outcome remains an intriguing one. We are pleased that Dr Howles and colleagues would agree with us that raised LH levels in IVF subjects are not deleterious to pregnancy outcome. Our data examined the patients as early as 6 days before the expected time of oocyte collection and, seemingly, well away from the time of an attenuated or obvious LH surge. As we emphasised in our article, the importance of serum LH in early pregnancy loss in patients with polycystic ovary syndrome is a different matter. Although we are not usually in the habit of quoting abstracted articles, as opposed to manuscripts, we agree that the issue of follicular phase LH increases in patients with recurrent early miscarriage is intriguing. Perhaps failure to precisely diagnose polycystic ovary syndrome amongst IVF patients may explain the high miscarriage rate following IVF, if this LH hypothesis is true.

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Listeriosis revisited: the role of the obstetrician

Dear Sir,

We read with interest the recent report by Buchdal *et al.* on *Listeria* infection in pregnancy (*Br J Obstet Gynaecol* (1990), **97**, 186–189), highlighting their series of three patients.

We report our experience of six pregnancies complicated by listeriosis. Infection was confirmed by maternal and neonatal cultures. Four of the infants recovered completely, and two were stillborn. Four women presented with diminished fetal movements and were found to have an abnormal cardiotocogram (CTG) which prompted urgent delivery by caesarean section. Two women presented in preterm labour. One of these was referred from another hospital, and although the fetal condition appeared normal before transfer, the fetus was dead on arrival. In the other, a flat and unreactive CTG in labour rapidly deteriorated to a terminal bradycardia and fetal death before intervention was possible. The CTG was abnormal in all five fetuses monitored immediately before delivery and commonly showed a flat unreactive trace without decelerations. Meconium staining was noted in four pregnancies. None of the women admitted to consumption of any of the foods known to be associated with listeria infection.

We emphasise the following points from our experience. (1) Decreased fetal movements was the presenting complaint in four women and may be a marker for intrauterine infection, prompting self referral and appropriate early intervention. (2) A flat CTG appears to be a common finding where there is fetal listeria infection; in two women the CTG deteriorated rapidly leading to fetal death, in the other four prompt delivery led to a successful outcome. (3) Preterm labour complicated by a maternal pyrexial illness should raise the possibility of fetal listeria infection, a history of ingestion of food with a recognised listeria association may be absent.

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BOOK REVIEWS

Cardiac Problems in Pregnancy. Diagnosis and Management of Maternal Fetal Disease. Second edition by Uri Elkayam and Norbert Gleicher. Alan R. Liss Inc. New York, 1989, 846 pages with figures and tables, $124.50

This is an unusual book in that it considers a single part of the body, the cardiovascular system in both the mother and fetus.

The benefits of this approach to the obstetricians are not obvious since, with the important exception of pre-pregnancy counselling of maternal and fetal risks in a patient with pre-existing congenital heart disease, the obstetrician does not usually think of maternal and fetal heart disease at the same time or in the same patient.

The second edition has expanded the book to cover exercise physiology, haemodynamic monitoring, thromoembolism and amniotic fluid embolism, anaesthesia, cardiopulmonary resuscitation, drug therapy and Doppler ultrasound in the fetus.

There are now over sixty authors and eight hundred pages. This has allowed rather sloppy editing to evolve. For example, the electrocardiogram is considered as a diagnostic approach to maternal heart disease in one chapter but the reader must look at the previous chapter on cardiac findings in normal pregnancy to discover that pregnancy itself alters the ECG. Again, Eisenmenger's syndrome is mentioned in several places in the book but the main description, in the section on congenital heart disease and pregnancy, does not consider possible mechanisms of shunt reversal; this is only discussed in the chapter on analgesia and anaesthesia during pregnancy. Why does the section on cardiac surgery during pregnancy also discuss the general manifestations of Eisenmenger's syndrome? Surgery is not applicable to this condition (except combined heart and lung transplant to which the authors do not refer).

Most information concerning heart disease in the mother and fetus is present in this book but the reader has to look for it. For example, the chapter by Moller and Pierpont on genetic causes of cardiac diseases is one of the best accounts available.

This is a book for library shelves rather than the individual purchaser, unless the obstetrician has very special interests.

Michael de Swiet

Turner Syndrome edited by Ron G. Rosenfeld and Melvin M. Grumbach. Marcel Dekker, Inc. New York, Basle, 1990, 552 pages with figures and tables, $150 (US and Canada) $180.00 (all other countries)

This book is a collection of papers presented at the third International Turner Symposium in San Francisco in 1988. The book is edited by two well known reproductive endocrinologists one a paediatrician, the other a gynaecologist. The book opens with a fascinating monologue on Turner's original description but thereafter the book is divided into five sections. The first section on genetics is complex and requires more than a basic knowledge of modern genetics laboratory technique to appreciate the data presented. This section is made more difficult to understand by the wide range of styles of writing. This tends to be a problem throughout this book and an unfortunate criticism of books based on symposia with very large numbers of contributors This particular volume has 76 contributors in its 552 pages. The section on natural history and associated anomalies is excellent and summarizes the current understanding of Turner's syndrome extremely well. Likewise the section on growth hormone secretion and bone cartilage development is important in the light of current interest in hormonal replacement therapy and the effect of long-term oestrogen on bone.

The section on growth plate biology and Turner's syndrome is fundamentally interesting. The section on endocrine treatment tends to be somewhat repetitive and the summaries of these sections could have been better. Finally, the last section on intellectual and psychological development is valuable and it is good to see a section devoted to this area of concern in patients who have congenital abnormalities or genetic abnormalities In summary, this book is a collection of papers which at about £120 would be unjustified for any individual to purchase. It does however bring together workers in this field in one volume and would be a valuable reference text in major libraries.

D. K. Edmonds

The Unstable Bladder edited by Robert M. Freeman and John Malvern. Wright, London 1989, 156 pages with figures and tables, £45.00

This volume stems from a symposium devoted to the subject of 'The Unstable Bladder' held in London in 1986; it is perhaps unfortunate that it has had so long a gestation period. Edited by two gynaecologists it draws together acknowledged experts not only from our own specialty, but also from urology, paediatrics, geriatrics, psychiatry, neurophysiology, neurosurgery, nursing and engineering and thus gives a very broad coverage of the subject.

Many of the contributions are excellent and give a thorough account of 'the state of the art' and review of relevant literature; particularly notable are those chapters on obstruction and detrusor instability, drug therapy, and behaviour modification techniques but others are superficial or unbalanced. The chapter on investigative techniques, for example, devotes a mere 9 lines to clinical assessment and give scant consideration to conventional urodynamic methods, yet six pages are given over to a description of urethral electrical conductance measurement, a technique that, whilst undoubtably an interesting development in this area, is far from having an established role in the investigation of the unstable bladder.

The inclusion of an appendix taken from the reports on 'Standardization of Terminology of Lower Urinary Tract Function' in this, and other monographs on urodynamics, is a trend to be discouraged. These reports represent, without question, a major move towards the standardization of urodynamic terminology and techniques, and the International Continence Society are to be applauded for this contribution. Nevertheless, they have been published elsewhere and the need to reproduce them further seen by several authors and editors in this field, seems inappropriate padding.

The book in general is well produced, and whilst some of the photographs have not reproduced well, the line diagrams and half tone drawings are clear and effective. Nevertheless, if the volume is aimed at those already working in the field of gynaecology then most would find that it adds little to existing literature; if it is aimed at those seeking to develop such an interest, then the subject matter is probably too narrow to justify its purchase, at 33p per page.

P. Hilton

Books received some of which may be reviewed at a later date

Oral Contraceptives and Breast Cancer edited by R. D. Mann. Parthenon Publishing, Carnforth, Lancs and New Jersey USA. 1990, 406 pages with figures and tables, £45.

Progress in Obstetrics and Gynaecology Volume 8 edited by John Studd. Churchill Livingstone, Edinburgh, 1990, 416 pages with 95 illustrations, £21.95.

Immunobiology of Normal and Diabetic Pregnancy edited by D. Andreani. G. Bompiani, U Di Mario, W. Page Faulk and A. Galluzzo. John Wiley & Sons, Chichester, New York, 1990, 329 pages, fully illustrated £35.

Infertility Surgery. A Multimethod Approach to Female Reproductive Surgery by John J. Stangel. Appleton & Lange, Norwalk, Connecticut, 1990, 396 pages fully illustrated, £83.45

Tubal Reconstructive Surgery by Ginter Sotrel. Lea & Febiger, Philadelphia, London, 1990, 281 pages fully illustrated £51.56.

Manual of Clinical Problems in Obstetrics and Gynaecology. Third edition, edited by Michel E. Rivlin, John C. Morrison and G. William Bates. Little, Brown and Company, Boston, Toronto, London, 1990, 600 pages, £9.95.

Interaction Strategies. An Introduction for Health Professionals. Second edition by Lyn Porritt. Churchill Livingstone, Edinburgh, 1990, 192 pages illustrated £7.50.

Collins Medical Dictionary Medical Quotations by John Daintith and Amanda Isaacs. Collins,

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COMMENTARY

Long term consequences of fetal deprivation

Since the seminal observations of Dugald Baird, and the many subsequent studies of widely different populations, there can be little doubt that the quality of pregnancy, and the size and viability of the fetus, are related to the health and nutritional state of the mother. Women in deprived circumstances have smaller babies with a higher morbidity and mortality, and that seems to be particularly true of women who are themselves stunted and ill-nourished because of a deprived upbringing.

While the truth of that generalization seems undeniable, the average clinician may be more struck by the numerous exceptions, and the association is only convincingly seen in large population groups. The view has therefore developed that the fetus is remarkably well protected from vagaries of its mother's diet, and that although the fetus of an ill-fed mother may be somewhat smaller than it should be, given good post-natal conditions it will recover from that temporary setback and progress to a normally grown adult. This was nowhere more clearly shown than in the famous Dutch famine where the population of the Western Netherlands was subject to extreme food shortage during the exceptionally severe winter of 1944–45 Where the second and third trimesters of pregnancy coincided with the famine the birthweight of infants was reduced by some 300 g, more in boys than girls, and fetal and infant mortality was increased. But the long term consequences were encouraging: males who were exposed to the famine *in utero,* when examined at age 19 for military service, seemed to have suffered no ill-effects either physical or intellectual. In contrast to those babies whose birthweight was reduced because of their mother's exposure to famine at the end of pregnancy, mean birthweight was normal where only the first trimester overlapped the famine, although an excess of preterm delivery, perinatal death and central nervous system malformation were noted (Stein *et al.* 1975).

Thus while those concerned with maternal care continue to emphasize the importance of good health and nutrition, there is a general feeling that the fetus is well able to take care of itself in unfavourable circumstances, and that even if it is a little less well-grown than it should be, once free of the constraints of the uterus it will usually catch up.

We may have been unduly complacent. There is now a growing body of evidence that damage may be done to the fetus, particularly perhaps in early pregnancy, which will not become apparent until that fetus reaches adult life.

Again it was Dugald Baird who sowed one of the first seeds when he suggested (Baird, 1980) that rates of anencephaly in Scotland seemed to be related to the period when the women having the anencephalics were themselves being born. That is to say, those girl fetuses who were subject to deprivation because, for example, of the effect of economic depression on their mothers, have been left with a defect which makes them more liable to produce anencephalic fetuses. Baird's evidence was not very convincing statistically but more straws are now blowing in the same direction. In a particularly thorough study of Dutch women who had been exposed *in utero* to the 1944–45 famine, Lumey (1988) has been able to show that those who were exposed only during the first half of intrauterine life, and who were themselves of normal birthweight and grew to normal adult size, are now having babies of lower birthweight, with an excess of small-for-gestational age infants Those women who were exposed to the famine only during the second half of intrauterine life are not affected.

Now there is evidence that cardiovascular disease in adult life may relate to early experience of deprivation, perhaps as a young child, but maybe as a fetus. Barker and Osmond (1987) have shown that the wide geographical difference within the United Kingdom in deaths from stroke relate most closely to the differences in maternal mortality at the time, 75 years earlier, when those stroke victims were born. They found a similar relation between the number of persons dying from ischaemic heart disease and both infant mortality at the time they were born, and birthweight (Barker and Osmond, 1986; Barker *et al.* 1989*a*). An inverse relation between birthweight, independent of gestational age, and blood pressure, both in children and adults (Barker *et al.* 1989*b*; Whincup *et al.* 1989) can only add to suspicion that early deprivation, perhaps *in utero,* can have long term functional effects.

That long term damage can be inflicted on a fetus which will only become manifest when that fetus becomes an adult was made dramatically apparent by the effect of diethylstilboestrol taken by the mother in early pregnancy (Holt & Herbst, 1981). The effects of more general deprivation, perhaps nutritional, are less clearly apparent and none of the findings given here, with the possible exception of the recent Dutch famine data analysed by Lumey (1988) provides cast iron evidence. But taken together they should be enough to arouse anxiety.

Further evidence is needed. Some will come from further follow-up of Dutch famine cohorts which is in progress (Lumey *et al.* 1989*a,b*) and it is to be hoped that Britain with its proud record of obstetric epidemiology will continue to make a major contribution. But it may be that if we are to understand the effect of detrimental influences occurring in early pregnancy, and which may not even be evident at birth, detailed long-term prospective studies will be needed.

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Immunoscintigraphy of endometriosis

S. H. KENNEDY, O. A. MOJIMINIYI, N. D. W. SOPER, B. J. SHEPSTONE, D. H. BARLOW

Summary. Twenty-eight women with suspected endometriosis or infertility, or both, received radiolabelled monoclonal antibody OC-125 $F(ab')_2$ fragments before surgery in a study to determine whether foci of pelvic endometriosis could be displayed with immunoscintigraphy. Immunoscintigraphy was positive in 22 women (16 with endometriosis, two with pelvic adhesions, one with pelvic inflammatory disease and one with normal pelvic findings) and negative in five women (two with endometriosis and three with normal pelvic findings). One woman developed a hypersensitivity reaction and, therefore, did not receive the radiolabelled fragments. The method had 89% sensitivity and 33% specificity for the diagnosis of endometriosis; it had 91% sensitivity and 60% specificity for the diagnosis of benign pelvic disease.

CA-125 is a membrane antigen expressed on a variety of gynaecological malignancies including most non-mucinous ovarian carcinomas (Kabawat *et al.* 1983a) and adenocarcinoma of the endocervix, endometrium and fallopian tube (Kabawat *et al.* 1983b). CA-125 is also expressed on endometriotic tissue (Barbieri *et al.* 1986). The antigen is probably a cell membrane glycoprotein with a molecular weight >200 000 daltons (Davis *et al.* 1986) although, in endometriosis, lower molecular weight immunoreactive determinants of 55 000 and 140 000 daltons have been described (Mojiminiyi *et al.* 1989).

CA-125 is recognized by a murine monoclonal IgG1 antibody, OC-125, raised against a cell line from an ovarian serous cystadenocarcinoma (Bast *et al.* 1981). Serum CA-125 levels, measured by immunoradiometric assay with OC-125, are elevated in women with ovarian carcinoma (Bast *et al.* 1983) and adenocarcinoma of the endocervix, endometrium and fallopian tube (Niloff *et al.* 1984). Levels of CA-125 can be mildly elevated in women with endometriosis, especially those with extensive disease (Barbieri *et al.* 1986; Giudice *et al.* 1986; Patton *et al.* 1986).

In-vivo, CA-125 expression is demonstrated by immunoscintigraphy using radiolabelled OC-125 $F(ab')_2$ fragments. Most ovarian carcinoma primary and metastatic sites are displayed by ^{131}I-labelled fragments (Chatal *et al.* 1987). Ovaries affected by endometriosis can also be displayed by ^{131}I-labelled OC-125 $F(ab')_2$ fragments, as reported in a preliminary study (Kennedy *et al.* 1988). The present paper completes the description of the preliminary study and reports a larger study with ^{111}In-labelled OC-125 $F(ab')_2$ fragments.

Patients and methods

In a preliminary study women with suspected endometriosis were recruited, with informed consent, to have immunoscintigraphy in the week preceding surgery. The only exclusion criterion was a history of allergy to foreign proteins. Advice regarding the need to avoid pregnancy was given where appropriate.

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The ^{131}I-labelled monoclonal antibody OC-125 F(ab')$_2$ fragments were obtained pre-labelled (CIS, UK). Thyroid and intestinal uptake of radioactive iodine were blocked with oral potassium iodide 120 mg daily (taken for 3 weeks from the day before immunoscintigraphy) and oral potassium perchlorate 400 mg daily (taken for 3 weeks from the day of immunoscintigraphy) Skin tests for hypersensitivity to mouse immunoglobulin were made before injection of the OC-125 fragments. Each woman received 1 mg OC-125 F(ab')$_2$ fragments labelled with 37–55·5 MBq (1–1 5 mCi) ^{131}I in 100 ml normal saline given intravenously over 20 min. Each woman was asked to drink large quantities of fluid and to empty her bladder frequently.

Planar scintigrams were obtained 3 and 5 days after the injection. Anterior, posterior and lateral pelvic and abdominal views were taken with a General Electric Maxi Camera, 400T fitted with a medium energy collimator and interfaced to a 11/34A computer with gamma 11 V 3·3 software. Each view was acquired over 5 min on a 128 × 128 pixel matrix using a 30% energy window centred on the 364 KeV peak of ^{131}I.

In the main study, women with infertility and/or suspected endometriosis were recruited and their informed consent was obtained. Immunoscintigraphy was performed in the periovulatory period, in the week before surgery, with similar methodology. The monoclonal antibody OC-125 F(ab')$_2$ fragments (CIS, UK) were supplied coupled to diethylene-triamine-penta-acetic acid (DTPA) in a sterile and pyrogen-free solution. Labelling was achieved by the addition of 37–74 MBq (1–2 mCi) ^{111}InCl to 1 mg antibody-DTPA solution which also contained 9 mg NaCl and 1 ml 0·1 M acetate buffer (pH = 5·0). Each woman received 55·5–74 MBq (1·5–2 mCi) labelled antibody, given by slow intravenous injection and was imaged 24 and 48 h after the injection. Views identical to those described above were taken with the same gamma camera but interfaced to a PCS 512+ computer (Nuclear Diagnostics) with MSC multi-user gamma 11 software. Each view was acquired over 5 min on a 128 × 128 pixel matrix using 20% and 15% energy windows centred on the 172 and 247 KeV peaks of ^{111}In respectively. The study had been approved by the Central Oxford Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee.

Serum CA-125 levels were also measured in blood samples, taken in the periovulatory period, using commercially available immunoradiometric assay kits (CIS, UK). Levels were expressed in arbitrary units based on a primary reference standard (Bast *et al.* 1983). An elevated level was defined as >35 U/ml.

With the exception of the first patient, the surgeon was unaware of the immunoscintigraphic findings at the time of surgery. Patient positivity, rather than lesion positivity, was used to determine true positive cases and a patient was considered positive if endometriosis was confirmed at the time of surgery in any of the lesions detected by immunoscintigraphy.

Results

Six women (mean age 33·8, SD 6·1 years) were recruited into the preliminary study. Their principal complaints were infertility in three and pain in the other three. One woman had previously had a total abdominal hysterectomy and left salpingo-oophorectomy for endometriosis. All six women had immunoscintigraphy; the procedure was well tolerated and there were no hypersensitivity reactions Subsequently, three laparoscopies and three laparotomies were undertaken. The results of the first two patients have been reported previously (Kennedy *et al.* 1988)

Four women with positive immunoscintigraphy had severe endometriosis with ovarian endometriomata, peritoneal disease and adhesions. Minimal uptake was found in one woman with a few peritoneal implants and in one woman with signs of early endometriosis, in the form of peritoneal blebs and increased vascularity.

Twenty-two women (mean age 31·1, SD 5·8 years) were recruited into the main study; their principal complaints were infertility in 14 and pain in the other eight. Two women had had a total abdominal hysterectomy and bilateral salpingo-oophorectomy previously for endometriosis; one of them developed a hypersensitivity reaction to the skin test and therefore did not have immunoscintigraphy. The 21 women who had immunoscintigraphy tolerated the procedure well and had no hypersensitivity reactions. Subsequently 20 laparoscopies and one laparotomy were undertaken

Immunoscintigraphy was positive in 16 women of whom 10 had endometriosis. Five of these women had minimal-mild disease and five moderate-severe disease, according to the revised AFS classification of endometriosis (The American Fertility Society 1985). The severity and anatomical localization of disease correlated well with the immunoscintigraphic findings, even when the AFS classification was largely attributed to adhesions

Of the six women with positive immunoscintigraphy but no evidence of endometriosis, three had pelvic adhesions, two had normal pelvic findings and one had probable pelvic inflammatory disease (PID). Positive immunoscintigraphy with normal surgical findings may be a true false positive result. Alternatively, immunoscintigraphy may be superior to laparoscopy in diagnosing microscopic endometriosis in visually normal peritoneum (Murphy *et al.* 1986). Immunoscintigraphy was negative in five women, of whom two had minimal endometriosis and three had normal pelvic findings.

In one woman with negative pelvic immunoscintigraphy, considerable uptake was demonstrated in the region of both kidneys. This woman had systemic lupus erythematosus without apparent renal involvement. The significance of such positivity can only be determined by further investigation.

Serum CA-125 levels were measured in 16 women (five with minimal-mild disease, five with moderate-severe disease, three with normal pelvic findings and three with adhesions or PID). The levels were only elevated (>35 U/ml) in two women: one with moderate-severe disease (50 U/ml) and one with probable PID (48 U/ml). Both these women had positive immunoscintigraphy. Of the remaining 14 women with normal serum CA-125 levels, all had positive immunoscintigraphy, except one woman with a normal pelvis.

Discussion

Endometriosis can be difficult to diagnose. Although laparoscopy is the best diagnostic method, it is too subjective an assessment (Dmowski 1987) and microscopic disease is missed (Murphy *et al.* 1986) which may explain how severe disease can be found less than one year after a normal laparoscopy (Kennedy *et al.* 1989). Laparoscopy also has significant associated morbidity and mortality.

A non-invasive diagnostic test would be useful and would allow screening of at-risk populations but a test with sufficient sensitivity and specificity awaits development. Measurement of serum CA-125 levels by immunoradiometric assay in women with endometriosis has shown a diagnostic sensitivity of only 14–53% (Barbieri *et al.* 1986; Patton *et al.* 1986; Pittaway & Fayez 1986). In the present study, the sensitivity of the assay for the 10 women with endometriosis tested was only 10% (1 of 10).

In the diagnosis of ovarian malignancy, immunoscintigraphy has shown potential as a non-invasive test. Radiolabelled antibodies directed against tumour-associated antigens congregate around areas of high antigen concentration. tumours are imaged by detection of radioactivity. The ovaries seem ideally suited for radionuclide imaging. They receive a large proportion of the cardiac output, second only to the kidneys on a weight related basis, and yet they are positioned away from the blood pool allowing a high tumour-to-blood ratio without the need for subtraction techniques.

The commonest monoclonal antibodies used in ovarian carcinoma imaging are those directed against placental alkaline phosphatase, CA-125 and human milk fat globulin (HMFG). Epenetos *et al* (1985) imaged four of six ovarian adenocarcinomas using an ^{111}In-labelled monoclonal antibody (H17E2) against placental alkaline phosphatase. In a prospective study of immunoscintigraphy in women with suspected ovarian carcinoma recurrence, Chatal *et al* (1987) reported a sensitivity of 76% (13 of 17) and a specificity of 79% (15 of 19) using ^{131}I-labelled OC-125 F(ab')2 fragments. In women with suspected ovarian carcinoma or recurrence, immunoscintigraphy accurately assessed the extent of malignancy in 37 of 39 women, using ^{123}I-labelled HMFG2 (Shepherd *et al.* 1987)

In gynaecology, immunoscintigraphy has been used almost exclusively to image ovarian malignancy. The first report of its use in benign ovarian disease described positive immunoscintigraphy in two women with ovarian endometriosis using ^{131}I-labelled OC-125 F(ab')2 fragments (Kennedy *et al* 1988).

In the present study, ^{131}I was used until ^{111}In became available. ^{111}In has several advantages as a radionuclide, especially in imaging benign pelvic disease. It has a shorter half-life (67·5 h) than ^{131}I (8·05 days), it produces lower energy photons which can be imaged with a medium energy collimator thereby improving image resolution and its radioactive dose is much lower. Uptake of ^{111}In is greater than ^{131}I as *in vivo* dehalogenation of iodine is avoided (Halpern *et al.* 1983).

Combining the results for all 27 women in the present study, the values for the sensitivity and specificity of immunoscintigraphy for diagnosing endometriosis were 89% (16 of 18) and 33% (3 of 9) respectively. For the diagnosis of benign pelvic disease, including peritoneal adhesions of unknown aetiology, the corresponding values were 91% (20 of 22) and 60% (3 of 5), respectively. The poor specificity for endometriosis arises because CA-125 is not an antigen specific to endometriosis. Its expression probably also reflects peritoneal inflammation: uptake of radiolabelled OC-125 fragments certainly occurs when only peritoneal adhesions are present and is increased in women with endometriosis when peritoneal adhesions are also present. However, in the investigation of infertility the non-specific attachment of OC-125 fragments may be an advantage in identifying those women with pelvic disease to whom priority should be given for a diagnostic laparoscopy.

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Localization of anti-endometrial antibody binding in women with endometriosis using a double-labelling immunohistochemical method

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Summary. Anti-endometrial antibody binding was localized using a double-labelling immunohistochemical method on frozen sections of endometrium taken from a woman without pelvic disease. Serum from 40 women with endometriosis was tested and, as controls, serum samples from 20 adult males and 20 umbilical cords. The method allowed compensation for endogenous immunoglobulins in endometrium and accurate localization of anti-endometrial antibody binding in the cytoplasm of the glandular epithelium. Significantly more women with endometriosis (14/40) were found to have anti-endometrial antibodies than controls (1/40) ($P<0{\cdot}001$; χ^2). There was no correlation between disease severity and the presence of anti-endometrial antibodies or the intensity of staining.

Anti-endometrial antibodies have been detected in the serum of women with endometriosis using immunodiffusion (Badawy *et al.* 1984), passive haemagglutination (Mathur *et al.* 1982; Chihal *et al.* 1986), immunofluorescence (Mathur *et al.* 1982; Wild & Shivers 1985) and an enzyme-linked immunoabsorbent assay (Kennedy *et al.* 1990).

Antibody binding, demonstrated by indirect immunofluorescence on isolated glandular preparations, occurs mainly in the cytoplasm of endometrial glands, without regard to the phase of the menstrual cycle (Wild *et al.* 1987). Immunofluorescence on sections, however, has the disadvantage that the surrounding morphology is difficult to assess as counterstains reduce fluorescence. By using an immunohistochemical technique that allows sections to be counterstained, antibody binding is better localized.

We used an indirect immunohistochemical technique to detect the site of anti-endometrial antibody binding. No previous study has compensated for endogenous immunoglobulins (Ig), mainly IgG, which are present in normal endometrium (Tourville *et al.* 1970). These also bind the anti-(human IgG) conjugated antibody used to detect anti-endometrial antibodies. We adapted the method described by Sternberger & Joseph (1979) of dual-coloured staining of two antigens to distinguish between endogenous Ig and anti-endometrial antibodies.

Methods

Serum samples were obtained from 40 women with endometriosis diagnosed at laparoscopy for pain or infertility or both. Disease severity was staged according to the revised AFS classifi-

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cation of endometriosis (The American Fertility Society 1985). Control sera were obtained from 20 male adults, and 20 samples of umbilical cord blood (10 male and 10 female). Sera were stored at −20°C until tested.

Endometrial tissue was obtained at hysterectomy from a woman with regular menstrual cycles and no evidence of pelvic disease; histological examination showed the tissue to be normal secretory endometrium. The fragments of tissue (10 mm^3) were snap frozen in liquid nitrogen and stored at −70°C. Cryostat sections 7 μm thick were mounted on glass slides, air-dried, wrapped in foil and stored at −20°C. After thawing, the slides were fixed for 10 min in acetone and washed for 5 min in phosphate buffered saline (PBS). All subsequent incubations were made in a wet-box at 22°C.

A modification of the dual-coloured indirect immunohistochemical method described by Sternberger & Joseph (1979) was used. The purpose of incubation with the first conjugated antibody was to label any endogenous immunoglobulins present. Sections were incubated for 45 min with 50 μl of a horse-radish peroxidase conjugated rabbit F(ab')$_2$ anti-(human IgG) antibody (Southern Biotechnology, USA) diluted 1/50 in PBS containing 1% bovine serum albumin (BSA). After two further washes with PBS, 50 μl PBS containing 0·06% of the substrate 3,3' diaminobenzidine (Sigma, USA) and 0·3% hydrogen peroxide (10 vols) were added yielding a brown reaction product.

Sections were then washed with PBS and incubated for 45 min with 50 μl undiluted patient or control serum (or PBS as a control) After two washes with PBS, sections were incubated for 45 min with 50 μl of an alkaline phosphatase-conjugated rabbit F(ab')$_2$ anti-(human IgG) antibody (Southern Biotechnology, USA), diluted 1/20 in PBS containing 1% BSA, followed by two further washes with PBS. Antibody binding was localized as a pink reaction product after incubation with a freshly prepared and filtered substrate mix containing 0·5 mg/ml naphthol AS-B1 phosphate (Sigma, USA) and 0·1 mg/ml of freshly diazotized New Fuchsin (Sigma, USA) in 0·05M Tris buffer, pH 8·7.

In preliminary work, incubation with the substrates alone showed a need to block endogenous alkaline phosphatase activity with levamisole (Sigma, USA) at 100 mM in the substrate mix. There was no need to block endogenous peroxidase as its activity could not be demonstrated in these sections.

Sections were labelled in duplicate, counterstained with haematoxylin and mounted in glycerin. Pink staining of glands was assessed as strong (positive), or faint or absent (negative) by two independent observers, both blind to patient details.

Results

The mean age of the women with endometriosis was 30·7 years (SD 4·8, range 20·7–39·8 years). The presenting complaints were pelvic pain in 11 (27·5%), infertility in 7 (17·5%) and pelvic pain with infertility in 22 (55%).

There was uniform brown staining indicating endogenous immunoglobulin throughout the stroma in all sections and negligible pink staining in the control sections incubated with PBS in place of serum. In sections incubated with serum, the pink staining of anti-endometrial antibody binding could clearly be localized to the cytoplasm of the glandular epithelium. This was because the immunohistochemical method provided good morphological detail and because the antigenic reactivity of the endogenous immunoglobulins in the endometrial stroma was blocked by enzyme product associated with the first peroxidase conjugated antibody. In many sections pink staining was confined to glands in the stratum functionalis with no binding to glands in the stratum basalis.

The proportion of subjects with anti-endometrial antibodies was significantly greater in the endometriosis group than in the control group ($P<0·001$, χ^2) The results are shown in Table 1. There was no correlation between staining intensity of the glands and disease severity.

Discussion

Weed & Arquembourg (1980) first suggested that endometriosis might be an autoimmune disease on the basis of their unpublished finding of complement component C3 detected by immunofluorescence in the endometrium of 'virtually all' women with endometriosis and not in those women free of the disease. Further evidence of complement involvement is that concentrations of complement components C3c and C4 detected by radial immunodiffusion in the serum and peritoneal fluid of women with endometriosis were found to be higher than in normal controls (Badawy *et al.* 1984). Other studies, however, have not confirmed these findings (Steele *et al.* 1984; Dunselman *et al.* 1988).

Table 1. Detection of anti-endometrial antibodies in the serum of women with endometriosis, staged according to the revised AFS classification, and in serum samples from adult males and umbilical cords using a double-labelling indirect immunohistochemical method

Serum samples	No of samples	Degree of staining		
		Absent	Faint	Strong
Adult/cord controls	40	17	22	1
Minimal-mild disease	30	6	13	11
Moderate-severe disease	10	3	4	3

Weed & Arquembourg (1980) speculated that menstrual proteins released from endometriotic tissue may be recognized as 'foreign', thereby triggering an immune response. Additional support for this theory of autoimmunity is provided by the demonstration in women with endometriosis of a variety of non-specific autoantibodies.

In women with endometriosis, levels of IgG autoantibodies against histones, nucleotides and phospholipids, including cardiolipin, were significantly higher than in a control population comprising 50 healthy women and 50 male blood donors (Gleicher *et al.* 1987). These authors concluded that finding a wide variety of auto-antibodies in endometriosis suggested polyclonal B-cell activation, a feature of autoimmune disease.

Organ-specific autoantibodies have also been reported in endometriosis. Sera from two of the three women with endometriosis tested by immunodiffusion produced precipitation lines against endometrial homogenates (Badawy *et al.* 1984). Using passive haemagglutination against extracts of sonicated endometrial (Mathur *et al.* 1982, Chihal *et al* 1986) and ovarian tissue (Mathur *et al.* 1982), women with endometriosis had significantly higher mean serum auto-antibody levels than controls. Chihal *et al* (1986) suggested this anti-endometrial antibody assay could be used as a screening test for endometriosis on the basis of 74% (17/23) sensitivity and 100% (28/28) specificity.

Anti-endometrial antibodies have also been demonstrated using immunofluorescence on frozen sections of endometrium. Sera from 12 of 13 women with endometriosis and none of 10 healthy female controls were positive after incubation with a fluorescein-conjugated rabbit anti-(human IgG) antibody (Mathur *et al.* 1982). In a similar study, 28 of 42 infertile women were found to have anti-endometrial antibodies; of these 28 women, 24 had endometriosis (Wild & Shivers 1985). No study has demonstrated a correlation between the severity of endometriosis and either the number positive for the test or the strength of fluorescence.

Data were not given in either of these papers on the location of antibody binding but in a subsequent study with indirect immunofluorescence of endometrial gland preparations binding was demonstrated in glandular epithelium cells, mainly in the cytoplasm (Wild *et al.* 1987) Antibody binding was eliminated by preabsorption of the serum with uterine tissue and there was no effect of the menstrual cycle on staining

In the present study, we have localized anti-endometrial antibody binding in histological sections with greater accuracy by using a method that compensates for endogenous Ig Patients known with certainty to be free of the disease were chosen as controls to test the method. It is unacceptable to use women without symptoms as controls if they have not had a laparoscopy because women with endometriosis can be asymptomatic. Even women with no evidence of endometriosis at laparoscopy could theoretically have the disease as microscopic endometriosis can exist in visually normal peritoneum (Murphy *et al.* 1986). The finding in the present study of one male control positive for anti-endometrial antibodies presumably represents cross-reactivity.

As immunohistochemistry is not a sufficiently quantitative method of measuring anti-endometrial antibody levels an enzyme-linked immunabsorbent assay was developed based on the findings of the present study (Kennedy *et al.* 1990). Mean anti-endometrial antibody levels were significantly higher in women with endometriosis than in a control population.

The production of anti-endometrial antibodies may be an innocuous event, unrelated to the pathogenesis of endometriosis. There is certainly no evidence that they have any adverse effect upon fertility despite speculation to the contrary (El-Roeiy *et al.* 1988). Nevertheless, their detection might have potential as a screening test for endometriosis and larger numbers of women are being investigated using the enzyme-linked immunoabsorbent assay.

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The implications of introducing the symphyseal-fundal height-measurement. A prospective randomized controlled trial

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Summary. A total of 1639 women attending the antenatal clinic of Gentofte University Hospital, Copenhagen, during 1986–1987 was randomized into a symphyseal fundal (SF)-group and a control group. The women in the SF-group had their fundal height measured from the 29th week until delivery. The measurements were used along with the other usual screening procedures. The SF-measurements were not found helpful in the prediction of small-for-gestational-age infants and no significant differences were found between the two groups regarding the number of interventions, additional diagnostic procedures, or the condition of the newborns.

A major goal of antenatal care is to detect and prevent intrauterine growth retardation (IUGR) by which we mean a condition that will lead to a small-for-gestational-age (SGA) infant. These SGA-infants, generally defined as infants with a birthweight below the 10th centile, have an increased risk of neonatal morbidity, mortality and impaired neurological development (Wennergren *et al.* 1988, Dijxhoorn *et al.* 1987). Even though not all infants in the SGA-group are growth retarded and some infants with appropriate-for-gestational age (AGA) birthweight may be growth retarded, SGA-infants still represent an at risk group. At the present state of the art of obstetrics it has not proven possible to accelerate intrauterine growth in the growth retarded fetus. As these fetuses are more susceptible to perinatal complications, it is of great importance to identify them antenatally and if necessary to terminate the pregnancy.

Several sophisticated technological methods, such as ultrasound and blood velocity measurements, have been adapted for detecting IUGR but they are not available as screening procedures in many hospitals. Around 50% of the SGA-infants are not detected antenatally (Rosenberg *et al.* 1982, Hepburn & Rosenberg 1986).

It has been claimed that measuring the fundal height is a good screening method for IUGR. The method is simple, easy to learn, and does not demand expensive equipment or time.

The predictive values of fundal height measurements have been studied by several investigators (Persson *et al.* 1986, Cnattingius *et al.* 1984 & 1985, Rosenberg *et al.* 1982, Wallin *et al.* 1981, Quaranta *et al.* 1981, Rogers & Needham 1985, Calvert *et al.* 1982, Belizan *et al.* 1978, Westin 1977) and were recommended for clinical use. Only Rosenberg *et al.* (1982) and Persson *et al.* (1986) found the symphyseal-fundal

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measurements (SF-measurements) to be of limited value as a screening method. Until now, however, no prospective controlled trials have been undertaken to assess the effect of introducing the method in antenatal care.

The aim of this study was to assess the influence of SF-measurements on the detection of SGA-fetuses antenatally, on interventions in the pregnancies involved and on fetal outcome. The study was undertaken in an obstetric department, which had not used SF-measurements as a screening procedure previously.

Subjects and methods

We estimated the sample size using the percentage of correct classification of SGA and AGA as a measure of outcome. In order not to overlook a 5% increase in accuracy from the 90% expected in the control group, almost 1000 pregnancies would be needed ($\alpha = 0{\cdot}05$ and $\beta = 0{\cdot}2$). Taking drop-outs into account we considered that we would need all the pregnant women attending our antenatal clinic in one year. The investigation was approved by the local ethics committee. All pregnant women attending the antenatal clinic during 1986 were therefore submitted prospectively to the trial, generally at about 14 weeks gestation. After receiving formal oral and written information 60 women did not want to participate. A further 27 were excluded before the allocation because of uncertain dates of delivery and no ultrasound examination had been conducted before 20 weeks (eight women) or because they had received antenatal care in another hospital (19 women). After the allocation 21 women with twin pregnancies were excluded (12 in the SF-group and nine in the control group) and so were 13 women with uncertain dates of delivery (seven in the SF-group and six in the control group). A further 60 women were excluded after allocation because antenatal care had taken place elsewhere (28 in the SF-group and 32 in the control group) and 36 were excluded because of miscarriage (17 in the SF-group and 19 in the control group).

The remaining 1639 women participated in the trial. They all had regular menstrual cycles with a known last period or had gestational age estimated by ultrasound before 20 weeks. On their first visit to the antenatal clinic the women were randomized into two groups by drawing a sealed opaque envelope containing a project number, which ranged from 1 to 1800. An uneven number resulted in an allocation to the SF-group and an even number to the control group.

SF-Group

This consisted of 804 women allocated to have SF-height measurements taken with a metric non-elastic tape, each time they visited their midwife or the obstetrician at the antenatal clinic from 28 weeks gestation. The results were plotted on a reference SF-growth chart and placed in the usual obstetric case record. Thus the method was used as a screening test along with the other usual screening procedures.

The SF-height was measured at least three times in 632 pregnancies (79%), once or twice in 121 (15%), but not at all in 51 pregnancies (6%).

Control group

This consisted of 835 women allocated to have SF-height measurements taken with a fabric tape with no marks. The tape was cut off and was not measured until after the delivery. The SF-height was measured at least three times in 655 pregnancies (79%), once or twice in 138 (16%) but not at all in 42 pregnancies (5%).

The SF-height was measured as described by Westin (1979) with the woman lying in the supine position, her legs straight, the uterus relaxed, an empty bladder and the fetus in a longitudinal position. The measurements were taken along the longitudinal axis of the uterus from the fundus uteri to the upper part of the pubic symphysis. Correction was made for the position of the leading part of the fetus in the pelvis as recommended by Westin (1979).

The reference SF-growth chart was derived from a population of 311 pregnant women from Copenhagen County and is used generally in the county. The 10th centile is taken as the lower limit of normal values and corresponds with the lower limit used by Westin (1977). An SF-curve was considered abnormal if it showed a fall of >20% for at least two consecutive values, or at least two values <10th centile, or the curve was static with at least three consecutive measurements with unaltered values (Wallin *et al.* 1981, Isager *et al.* 1985).

These guidelines were agreed upon by the staff before the trial started, but as we can see retrospectively, they were not always followed.

The usual screening procedures in the obstet-

Table 1. Characteristics before pregnancy in the two groups

Factor	SF-group (*n*=804) *n*	(%)	Control (*n*=835) *n*	(%)
Parity				
0	431	(54)	438	(52)
1	280	(35)	288	(34)
2	76	(9)	88	(11)
3	12	(1)	14	(2)
>3	5	(0·6)	7	(0·8)
Maternal age (years)				
<20	18	(2)	13	(2)
20–29	431	(54)	466	(56)
30–39	339	(42)	341	(41)
>39	16	(2)	15	(2)
Previous deliveries				
SGA-infants	19	(2)	18	(2)
Birthweight <2500 g (unknown gest.age)	5	(0·6)	4	(0·5)
Perinatal death	7	(0·9)	8	(1)
Smoking				
> 9 cigarettes/day*	160	(20)	156	(19)
Alcohol consumption				
> 5 drinks/day*	6	(0·7)	6	(0·7)
Maternal weight class†				
Slender	294	(36)	315	(38)
Normal	431	(54)	441	(53)
Slight overweight	61	(8)	60	(7)
Severe overweight	16	(2)	16	(2)
Unknown	2	(0·2)	3	(0·4)

*At the first visit to the antenatal clinic.
†Body mass index (National Food Agency of Denmark 1987) in the non-pregnant state.

ric department included measurement of placental lactogen hormone in the 34th week, taking the 2·5 centile as the lower limit of normal (Lindberg & Nilsson 1973); fetal weight estimate from the 29th week, using the 10th centile in the growth chart from the Danish National Board of Health (1976) as the lower limit of normal; maternal weight gain during pregnancy, regarding an average weight gain of <250 g in 4 weeks as suspicious.

If any other diagnostic procedures or treatments were prescribed due to suspicion of IUGR, the pregnancy was categorized as 'suspected IUGR'. Diagnostic procedures indicated for suspected IUGR were ultrasound measurements of biparietal diameter and cardiotocography (a non-stress test).

The newborns were classified as SGA if the birthweight was <10th centile (The Danish National Board of Health, 1976). All compromised infants were transferred to the intensive neonatal ward, situated in another hospital in the county.

For calculation of significance, the χ^2-test was used (limit of significance: $P<0·05$). The 95% confidence intervals are shown in parenthesis.

Results

There were only minor differences between the two groups in characteristics before pregnancy (Table 1), and in the course of the present pregnancy with regard to the prevalence of hydramnios (>1·5 litres) (nine in the SF-group and seven in the control group) and of bleeding (89 in the SF-group and 94 in the control group). Albuminuria occurred in 26 pregnancies in the SF-group and in 24 in the control group. Hypertension, both essential and pregnancy-induced (after 20 weeks), was found in 35 pregnancies in the SF-group and in 33 in the control group.

Suspicion of IUGR arose in 10% of the pregnancies in both groups (83 in the SF-group and 85 in the control group). In almost half of these

Table 2. Prediction of SGA-infants in the SF-group compared with the control group

	SF-group (*n*=804)		Control (*n*=835)		SF−Control (%)	(95% CI)
Sustained suspicion of IUGR *n* (%)	42	(5·0%)	49	(6·0%)	−0·6	(−2·9 to 1·6)
SGA-infants *n* (%)	61	(7·6%)	48	(5·7%)	1·8	(−0·6 to 4·3)
Predictive value of pathological variable	17/42	(40·5%)	23/49	(46·9%)	−6 5	(−27·2 to 14·3)
Predictive value of normal variable	718/762	(94·2%)	761/786	(96 8%)	−2 6	(−4·7 to −0·5)
Sensitivity	17/61	(27·9%)	23/48	(47·9%)	−20·1	(−38·5 to −1·6)
Specificity	718/743	(96·6%)	761/787	(96·7%)	−0·1	(−1·9 to 1·8)
Accuracy	735/804	(91·4%)	784/835	(93·9%)	−2·5	(−5·0 to 0·1)

SGA, small-for-gestational age. SF, symphysis fundal height. IUGR, intrauterine growth retardation.

Table 3. Diagnostic procedures and interventions due to suspicion of intrauterine growth retardation

	SF-group (n=804)		Control (n=835)		SF−Control (%)	
	n	(%)	n	(%)	(95% CI)	
Sick-leave	10	(1·2)	12	(1·4)	−0·2	(−1·3 to 0·9)
Hospitalized	15	(1·9)	8	(1·0)	0·9	(−0·2 to 2·1)
Induction of labour	17	(2·1)	21	(2·5)	−0·4	(−1·9 to 1·1)
Caesarean section						
Elective	4	(0·5)	7	(0·8)	−0·3	(−1·1 to 0·5)
Emergency	5	(0·6)	6	(0·7)	−0·1	(−0·9 to 0·7)
CTG (non-stress test)	48	(6·0)	50	(6·0)	−0·02	(−2·3 to 2·3)
Ultrasound (BPD)	59	(7·3)	60	(7·2)	0·2	(−2·4 to 2·7)

No significant differences between the two groups were found (P>0·05).
CTG, cardiotocography BPD, fetal biparietal diameter.

suspicion was withdrawn before delivery (Table 2), leaving 42 (5%) in the SF-group and 49 (6%) in the control group. Table 2 shows the predictive values, sensitivity, specificity, and accuracy of suspicion or no suspicion of IUGR. The difference between the sensitivities was −20% (95% CI −38·5 to −1·6) and the difference between the predictive values of no suspicion of IUGR was −2·6% (−4·7 to 0·5), favouring the control group.

There were no significant differences between the two groups in respect of diagnostic procedures and interventions due to suspicion of IUGR (Table 3). Neither were there any significant differences in fetal outcome. The number of SGA-infants, perinatal deaths, and infants transferred to neonatal ward were similar in the two groups (Table 4), and the diagnoses from the neonatal ward did not show any significant differences (Table 5). Of the 109 SGA-infants, 23 (21%, 95% CI 13 to 29) were transferred to the neonatal ward, compared with 4% (95% CI 3 to 5) of the AGA infants. Eleven (48%) of the transferred SGA-infants were born before 36 completed weeks.

There were 11 perinatal deaths (Table 4): two infants had major malformations, two had umbilical cord complications and one was found to have a serious placental insufficiency. One infant died 2 days after birth because of thrombosis of the inferior caval vein; five intrauterine deaths were unexplained.

Table 4. Fetal outcome

	SF-group (n=804)		Control (n=835)		SF−Control (%)	
	n	(%)	n	(%)	(95% CI)	
Girls	406		403			
Boys	396		430			
Sex unknown	2		2			
Major malformations	13	(1·6)	19	(2·2)	−0·7	(−2·0 to 0·7)
SGA	61	(7·6)	48	(5·7)	1·8	(−0·6 to 4·3)
Apgar score at 1 min						
<4	9	(1·0)	10	(1·0)	−0·1	(−1·1 to 1·0)
<8	96	(12·0)	103	(12·0)	−0·4	(−3·6 to 2·8)
Apgar score at 5 min						
<4	4	(0·5)	4	(0·5)	0·02	(−0·7 to 0·7)
<8	10	(1·0)	11	(1·0)	−0·1	(−1·2 to 1·0)
Umbilical artery blood						
pH<7·15	25/196		36/201		−5·2	(12·3 to 1·9)
Perinatal deaths	6	(0·7)	5	(0·6)	0·2	(−0·7 to 0·9)
Transferred to neonatal ward	43	(5·4)	42	(5·0)	0·3	(−1·8 to 2·5)

SGA, Small-for-gestational-age.
No significant differences between the two groups were found (P>0·05).

Table 5. The final diagnosis on the 85 infants, transferred to the neonatal ward

	SF-group (n=43)		Control (n=42)		SF−Control (%) (95% CI)	
	n	(%)	n	(%)		
SGA	11	(25·6)	12	(28·6)	−3·0	(−22·2 to 16·2)
Dysmature	8	(18·6)	8	(19·0)	−0·4	(−17·3 to 16·4)
Asphyxia	15	(34·9)	8	(19·0)	15·8	(− 3·3 to 35·0)
RDS	10	(23·3)	8	(19·0)	4·2	(−13·4 to 21·8)
Preterm	20	(46·5)	19	(45·2)	1·3	(−20·2 to 22·8)
Aspiration	5	(11·6)	6	(14·3)	−2·7	(−17·1 to 11·8)
Sepsis	5	(11·6)	4	(9·5)	2·1	(−11·2 to 15·4)
Hyperbilirubinaemia	8	(18·6)	7	(16·7)	1·9	(−14·5 to 18·4)
Hypoglycaemia	9	(20·9)	8	(19·0)	1·9	(−15·4 to 19·1)
Malformations	9	(20·9)	5	(11·9)	9·0	(− 7·0 to 25·0)
Seizures	1	(2·3)	2	(4·8)	−2·4	(−10·4 to 5·5)

SGA, Small-for-gestational age. RDS, respiratory distress syndrome.

Discussion

The object of searching for IUGR in antenatal care is, of course, to obtain ‘better and bigger babies’. Once IUGR is suspected, our means of correcting this condition are limited and have not been shown to be effective. The available means are intensified surveillance or termination of pregnancy to prevent perinatal death or severely affected infants.

The hypothesis, that introduction of SF-measurements would give a more accurate prediction of SGA-infants in the SF-group, was not proven, with a risk of 20% of overlooking a difference in accuracy of 3% or more. In fact we found better sensitivity and better prediction of the AGA-infants in the group with masked measurements.

There was no difference in the number of pregnancies in which suspicion of IUGR arose, and consequently we did not find more diagnostic procedures and interventions due to suspicion of IUGR in the SF-group.

The introduction of SF-measurements did not influence fetal outcome. With the sample size in this investigation, we had a 20% risk of overlooking a 3% difference in the number of SGA-infants and infants transferred to the neonatal ward, and a risk greater than 60% of overlooking a decrease in perinatal mortality up to 0·1%. Though the SF-measurements were of no diagnostic assistance in the antenatal clinic in this investigation, the lack of statistical significance does not necessarily mean, that SF-measurements have no diagnostic value in themselves.

In the SF-group the SF-measurements may have been influenced by the knowledge of gestational age and fetal weight estimates Before initiating this trial we plotted the fetal weight estimate against SF-measurements and found no correlation. These values were taken from a retrospective pilot study. Thus, in a clinical setting, the measurements may be influenced by the general impression of the fetus being normal or SGA. If so, masked SF-measurements, as in our control group, should give better predictive values than SF-measurements in the SF-group, if the measurements have any additional value in detecting IUGR. The value of a diagnostic method will depend on the general clinical circumstances into which it is introduced. The beneficial effect of a screening method, such as SF-measurements, on neonatal condition depends not only on the predictive values of the method, but also on the value of the additional diagnostic procedures, the proper reaction to pathological values, and the possibilities of correcting or preventing adverse outcomes.

Even though we have not shown any improvement of the condition of the newborn it may still be important to be able to predict the birth of a SGA-infant as accurately as possible.

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New design rigid and soft vacuum extractor cups: a preliminary comparison of traction forces

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Summary. Women due for vacuum extraction were randomly allocated to delivery using one of two soft cups (Silc or Silastic) or two new design rigid cups (New Bird or O'Neil). Traction forces were recorded continuously and higher values were reached with the rigid than the soft cups (median 15·8, range 7·5–19·7 *vs* 11·1, 7·2–15·1 kg, $P<0{\cdot}01$). Selection of the most appropriate vacuum cup for each clinical situation should take into account that the flexible cups are associated with less cosmetic disfigurement but have a lower capacity for traction.

During the past 30 years, the use of the obstetric vacuum extractor has gained wide acceptance in continental Europe and Scandinavia, but not in most English-speaking countries (Vacca *et al.* 1983). There is considerable overlap of the indications for vacuum extraction and forceps delivery, and in many cases the choice of instrument is a matter of operator preference.

There is consensus that maternal trauma resulting from vacuum extraction is less than that from forceps delivery (Ryden 1986; Johanson *et al.* 1989). Problems associated with the use of vacuum extraction have included suction tubing leakage, detachment of the vacuum cup, and fetal trauma and temporary cosmetic disfigurement (Chamberlain 1980). Meta-analyses of randomized comparisons of vacuum extraction with forceps delivery have shown vacuum extraction to be associated with more delivery failures (odds ratio 2·55, 95% confidence intervals 1·60–4·07), less use of regional or general anaesthesia (0·33, 0·22–0·48), less significant maternal injury (0·38, 0·24–0·58), a greater frequency of cephalhaematoma (2·49, 1·31–4·72), fewer other scalp injuries (0·44, 0·25–0·79), a trend to more 5-min Apgar scores <7 (1·77, 0·97–3·23) and more maternal worries about the baby (2·80, 1·07–7·35) (Keirse 1988).

Follow-up of the offspring of one randomized trial at 9 months of age revealed no significant differences between the two groups (Carmody *et al.* 1986a).

Recent modifications of vacuum cup design may reduce certain of the problems associated with vacuum extraction. The new Bird cup (AB Vacuum Extractor, Gothenburg) and the O'Neil cup (Go Medical, Subiaco) are rigid cups modified to reduce the 'tilting' force when the direction of traction is not perpendicular to the cup. The chance of tubing leaks is reduced by separation of the suction and traction mechanisms. The O'Neil cup has been compared with the Malmstrom cup with no difference in neonatal outcome being shown (Thiery *et al.* 1987). A randomized comparison of the new Bird cup with the original Bird cup showed similar outcomes except an increase

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in neonatal jaundice and a trend towards more cup detachments with the new design (Carmody *et al.* 1986b).

While the major objective of the new designs of rigid cup is to reduce the likelihood of delivery failure, that of the new 'soft' cups is to reduce the disfiguring effect of the procedure on the fetal scalp. Two examples are the Silc cup (Menox AB, Gothenburg) and the Silastic cup (Dow Corning, Midland MI).

Because of their fundamentally different mechanisms of action, it is important that comparative studies of rigid and soft vacuum cups be performed to enable obstetricians undertaking vacuum delivery to select the instrument most appropriate to the clinical situation.

Under laboratory conditions using a canine skin covered sphere model, the average traction at 550–600 mm Hg vacuum achieved with the 60 mm Bird cup, the 65 mm silastic cup and the 60 mm Mity-Vac cup (Columbia Medical-Surgical, Bend, OR) were 19, 20 and 18 kg respectively (Duchon *et al.* 1988). The clinical relevance of this model has been questioned (Schwartz 1988), and comparative *in vivo* traction force measurements have not to our knowledge been reported.

One randomized clinical comparison of the conventional Malmstrom and the Silastic cup has shown shorter extraction times and fewer scalp injuries, but more extraction failures with the latter (Hammarstrom *et al.* 1986).

In another trial comparing various metal cups with the Silc cup, the excess of failures with the latter group was not statistically significant (Cohn *et al.* 1989). It is not clear whether the failure rate in the metal cup group may have been influenced by the use of cups as small as 40 mm.

Of central importance to vacuum extraction is the amount of traction which may be applied to assist delivery. We have compared the traction forces achieved using the new design rigid vacuum cups with those using two designs of soft cup.

Subjects and methods

The study was undertaken at Coronation, Baragwanath and Johannesburg hospitals, and was approved by the committee for research on human subjects of the University of The Witwatersrand.

Women in labour at term who required vacuum delivery were asked to participate in the study and to sign informed consent. After baseline clinical details had been recorded, they were randomly allocated by means of previously 'shuf-

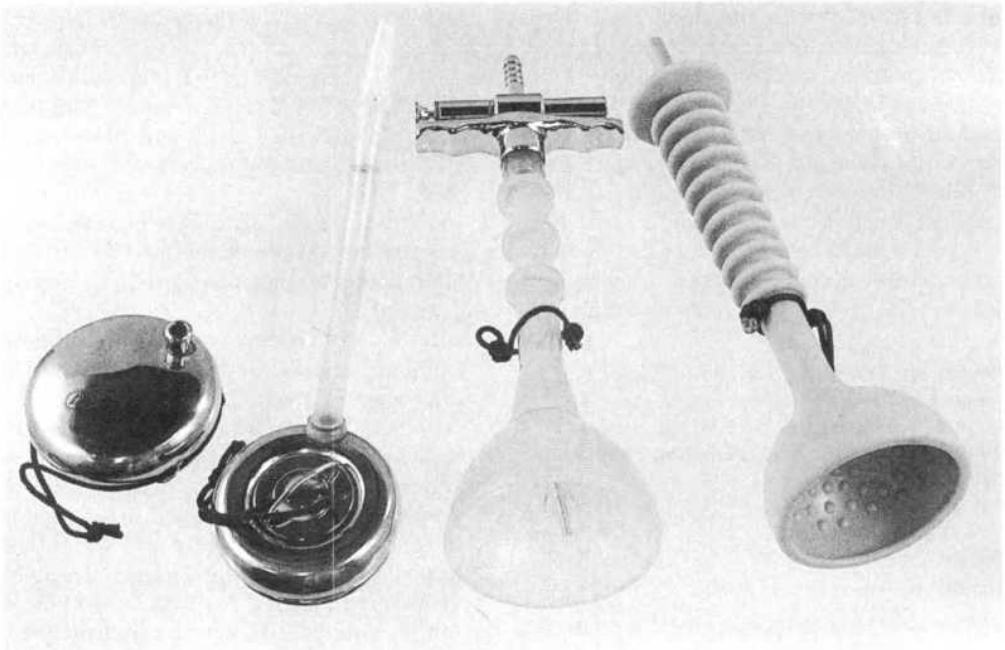

Fig. 1. From left to right, the new Bird, O'Neil, Silastic and Silc vacuum extractor cups. The cords attached to the handles of the two soft cups were used to adapt their use to the modified traction handle.

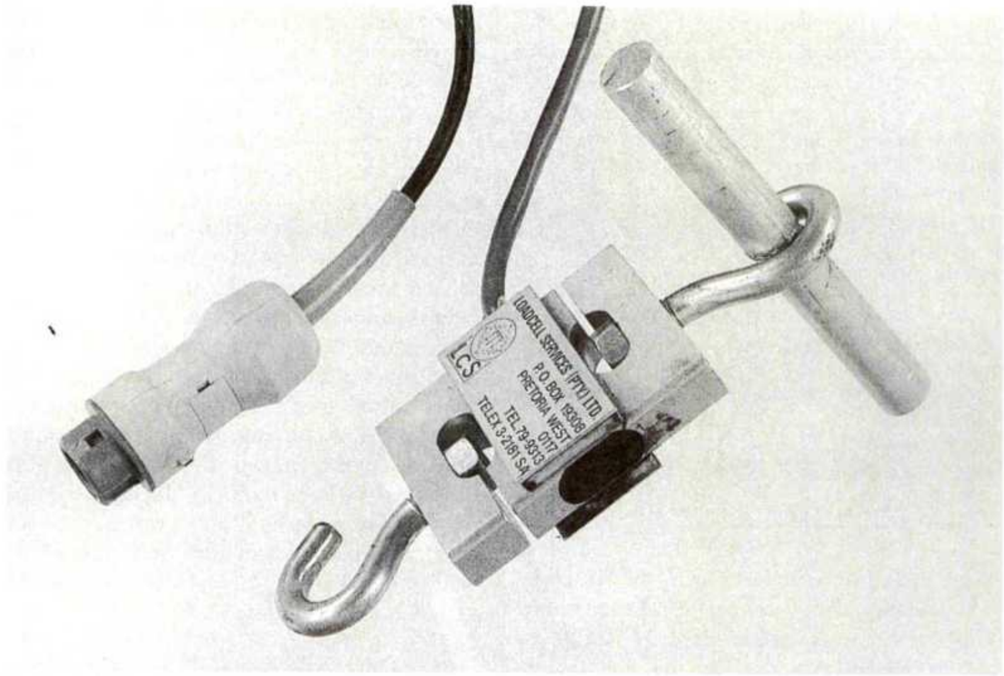

Fig. 2. The traction handle modified to incorporate a commercial loadcell. The signal was recorded, after appropriate amplification, on the tocograph channel of a Hewlett Packard 8040 A cardiotocograph.

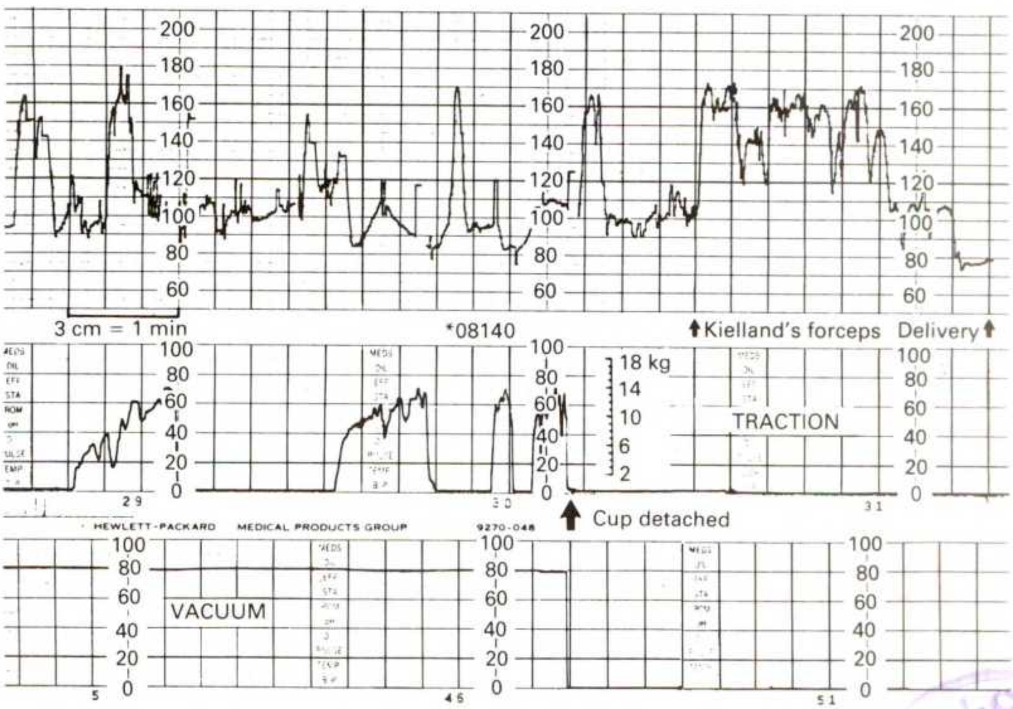

Fig. 3. Composite recording showing fetal heart rate (upper panel), traction force (middle panel) and negative pressure (lower panel), which clearly defines the point at which cup detachment occurred.

Table 1. Baseline characteristics of the two study groups

	Soft cup (n=13)	Rigid cup (n=18)
Age (years) median (range)	22(16–38)	24(19–42)
Nulliparous n (%)	8(62)	7(39)
Occipito anterior position n (%)	7(54)	9(50)
Caput succedaneum present n (%)	4(31)	6(33)
Indication for vacuum extraction: n (%)		
Previous caesarean section	3(23)	7(39)
Hypertension	3(23)	5(28)
Fetal distress	1(8)	
Poor progress in second stage	6(46)	6(33)

fled', sealed cards to delivery using the Silc cup, the Silastic cup, the 60 mm new Bird cup or the O'Neil cup (57 mm diameter) (Fig. 1). The allocated cup was used in all cases, and no women were withdrawn after enrolment.

Vacuum extraction was performed with the patient in the lithotomy position, using routine techniques. Vacuum pressures of approximately 600 mm Hg were used. The traction force applied during delivery was measured by means of a loadcell (Loadcell Services, Pretoria) incorporated into the traction handle (Fig. 2) and continuously recorded on the tocograph channel of an HP 4080 cardiotocograph (Hewlett Packard). After delivery, the recording system was calibrated by suspending a series of known weights from the traction handle. The timing of decompression and episodes of loss of vacuum were recorded either by means of a foot-switch connected to the cardiotocograph event marker, or automatically by means of a pressure transducer recording the vacuum pressure on the tocograph channel of a second cardiotocograph, the two recordings being synchronized by means of a common event marker (Fig. 3). Five minutes after delivery, the appearance of the baby's scalp was mapped on a standardized chart using symbols to indicate areas of rim marking, excoriation, oedema, bruising and cephalhaematoma. Because of the characteristic appearance of the rigid cup chignon, the assessor was aware of which type of cup was used. Baseline variables were compared to confirm uniformity of the groups, and outcome variables were compared using the Mann-Whitney test for continuous variables and the 95% CI of the odds ratio for proportions (Chalmers 1988).

Results

The use of separately 'shuffled' sets of allocation cards at the three hospitals resulted in a chance excess of patients allocated to the two rigid cup

Table 2. Results of delivery using soft or rigid vacuum extraction cups

	Soft cup (n=13)	Rigid cup (n=18)	Odds ratio	95% CI
Maximum traction force (kg)	11·1(7·2–15·1)	15·8(7·5–19·7)*		
Force at time of vacuum loss (kg)	10·0(8·4–14·6)	13·4(9·3–19·7)†		
Cup detached				
Overall	5(38)	1(5·6)	7·69	1·30–45·4
Occiput anterior	1(14) (n=7)	1(11) (n=9)	1·31	0·07–23·7
Occiput lateral or posterior	4(67) (n=6)	0(—) (n=9)	24·1	2·52–230
Failed vacuum delivery	3(23)	0(—)	12·9	1·20–138
1-min Apgar score <8	3(23)	4(22)	1·05	0·20–5·62
5-min scalp examination:				
Rim mark	3(23)	15(83)	0·09	0·02–0·38
Oedema	9(69)	18(100)	0·07	0·01–0·57
Bruising	9(69)	12(67)	1·12	0·25–5·03
Haematoma	0(—)	1(6)	0.18	0·003–9·49

Results are expressed as median values (range) or n (%) as appropriate. Significance of difference *$P<0·01$, †$P<0·05$ (Mann-Whitney).

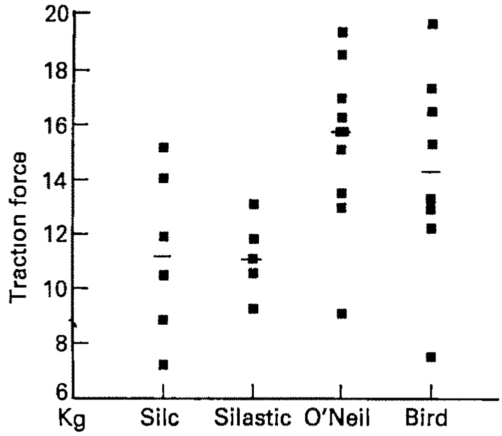

Fig. 4. Maximum traction forces measured using the two soft and two rigid vacuum extractor cups, with median values for each (–).

groups. However, the groups were adequately matched for the comparisons made (Table 1).

The outcome variables are shown in Table 2 and Fig. 4. The median of the highest traction forces reached was significantly higher for the rigid than the flexible cups. Loss of vacuum occurred on nine occasions with the soft cups in six women and on 10 occasions with the rigid cups in seven women and at significantly higher median traction force.

Discussion

The numbers in this preliminary study are too small to permit meaningful quantitative conclusions. However, the primary objective was to measure the traction forces achieved, which were clearly greater using the rigid than the soft cups. This finding is consistent with the increased failure rate using soft cups reported by Hammarstrom *et al.* (1986), and is at variance with the vitro findings of Duchon *et al.* 1988).

During traction on both the soft cups, the central part of the cup tended to 'tent' away from the fetal skull, suggesting that although the cup covered a large area of fetal scalp, traction forces on the scalp were disproportionately concentrated on a smaller area near the centre of the cup. Redesign of the cups with a more rigid central area to distribute the traction force more widely may obviate this problem.

We conclude that greater traction forces can be achieved using rigid than soft vacuum extractor cups. However, when the traction needed is likely to be modest, the advantage of reduced scalp disfigurement may favour the use of the soft cups.

Acknowledgments

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Preliminary Doppler studies on the uterine artery and myometrium in trophoblastic tumours requiring chemotherapy

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Summary. The uterine circulation in 38 patients with invasive mole or choriocarcinoma were investigated using Doppler ultrasound. Twenty-six non-pregnant and 23 pregnant volunteers were assessed in a similar fashion to act as control groups. The pulsatility indices were significantly lower in the patients with trophoblastic disease when compared with the non-pregnant and pregnant groups (Student's *t*-test; $P<0.001$ and $P<0.02$ respectively). The uterine circulation in persistent trophoblastic diseases shows a characteristic Doppler profile suggesting the presence of large low resistance blood vessels. This may be useful in the initial assessment of these tumours before cytotoxic chemotherapy.

Invasive mole and choriocarcinoma are infrequent sequelae to hydatidiform mole (Bagshawe *et al.* 1986). Yet they are important tumours as they occur in young women and are rapidly fatal without adequate treatment. The introduction of cytotoxic chemotherapy and the mole follow-up system have produced an overall cure rate for these trophoblastic tumours of 95% (Newlands *et al.* 1986). The main centre of treatment of these diseases in the United Kingdom is at the Charing Cross Hospital, London, where three chemotherapeutic regimens are used, ranging from low to high toxicity. The treatment protocol administered is determined by the risk of a patient developing drug resistance as assessed by a scoring system based on clinical and biochemical variables (Bagshawe 1976). Thus, curative chemotherapy can be instituted without exposing every patient to the toxicity associated with multiple agent chemotherapy. However, a small proportion of women with trophoblastic tumours still die despite this system. Adequate initial chemotherapy is important as patients who have relapsed have a reduced cure rate with subsequent treatment (Newlands *et al.* 1986). Thus, it is still necessary to examine methods by which trophoblastic tumours may be investigated so that management may be further optimised. We present the Doppler characteristics of the uterine circulation in trophoblastic tumours requiring chemotherapy and compare them to those of the pregnant and non-pregnant state.

Patients and methods

Thirty-eight consecutive patients referred for

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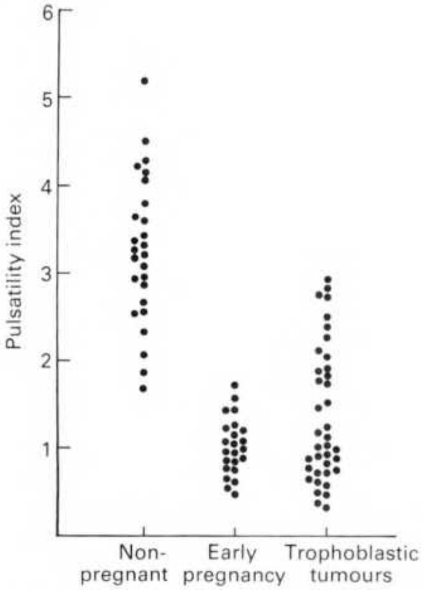

Fig. 1. Pulsatility indices of patients with trophoblastic tumours (mean 1·37, SD 0·73), subjects in early pregnancy (mean 1·00, SD 0·32) and in non-pregnant volunteers (mean 3·25, SD 0·83).

first line chemotherapy for trophoblastic tumours over a one year period were assessed before initiation of treatment. Twenty-six non-pregnant and 23 pregnant volunteers at between 10 and 16 weeks gestation were examined using an identical method. The non-pregnant subjects were recruited from hospital staff and from women referred for upper abdominal ultrasound which did not reveal any abnormality. They had regular menstrual cycles, were not taking any hormonal preparations and did not have a history of gynaecological problems. The pregnancy group were recruited from women referred for booking in the antenatal clinic. Each control subject had a real time ultrasound scan to detect any unknown pelvic abnormalities and to ascertain gestational age if pregnant. The mean ages of the non-pregnant, pregnant and trophoblastic disease groups were 27·7 (SD 8·0), 28·1 (SD 5·1) and 26·5 (SD 6·2) years respectively.

All investigations used a Diasonics DRF 400 pulsed Doppler duplex scanner with a 3·5 MHz probe with an on-line spectrum analyser. Each subject was required to rest for 5 min before the ultrasound scan and to have a full bladder. The uterine artery waveform was detected in the transverse plane adjacent to the supravaginal portion of the cervix as described previously (Long *et al.* 1989). The myometrium was sampled in several transverse and longitudinal planes. The time-velocity waveforms were analysed using the pulsatility index (PI) (Gosling, 1976).

Results

Pulsatility index

The PI of the uterine artery in the trophoblastic disease group (mean 1·37, SD 0·73) varied from values at the lower end of the range for non-pregnant subjects (mean 3·25, SD 0·83) and throughout the values obtained in early pregnancy (mean 1·00, SD 0·32) (Fig. 1). Doppler time velocity waveforms from the uterine artery in normal subjects, early pregnancy and a trophoblastic tumour are shown in Fig. 2. The values obtained for the women with trophoblastic disease were significantly different from both those obtained in the non-pregnant and pregnant groups (Student's *t*-test; $P<0\cdot001$ and $P<0\cdot02$ respectively). Similarly there was a significant difference

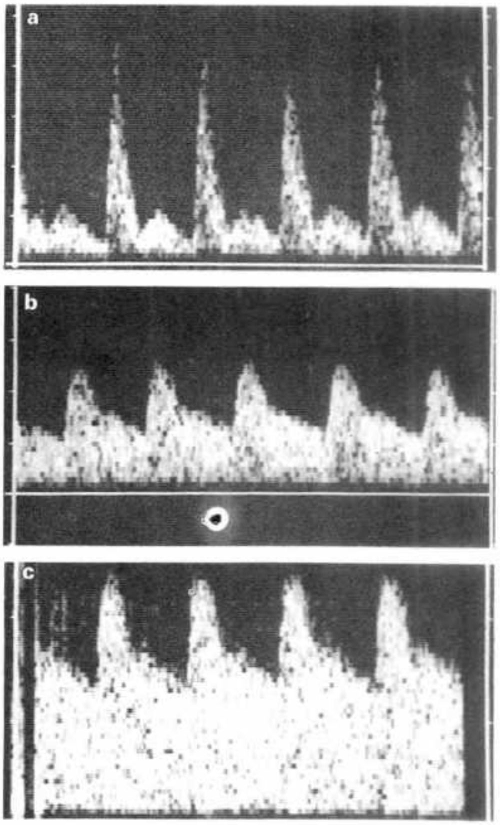

Fig. 2. Doppler frequency shifted spectra of the uterine artery in (a) normal subjects, (b) early pregnancy and (c) a trophoblastic tumour.

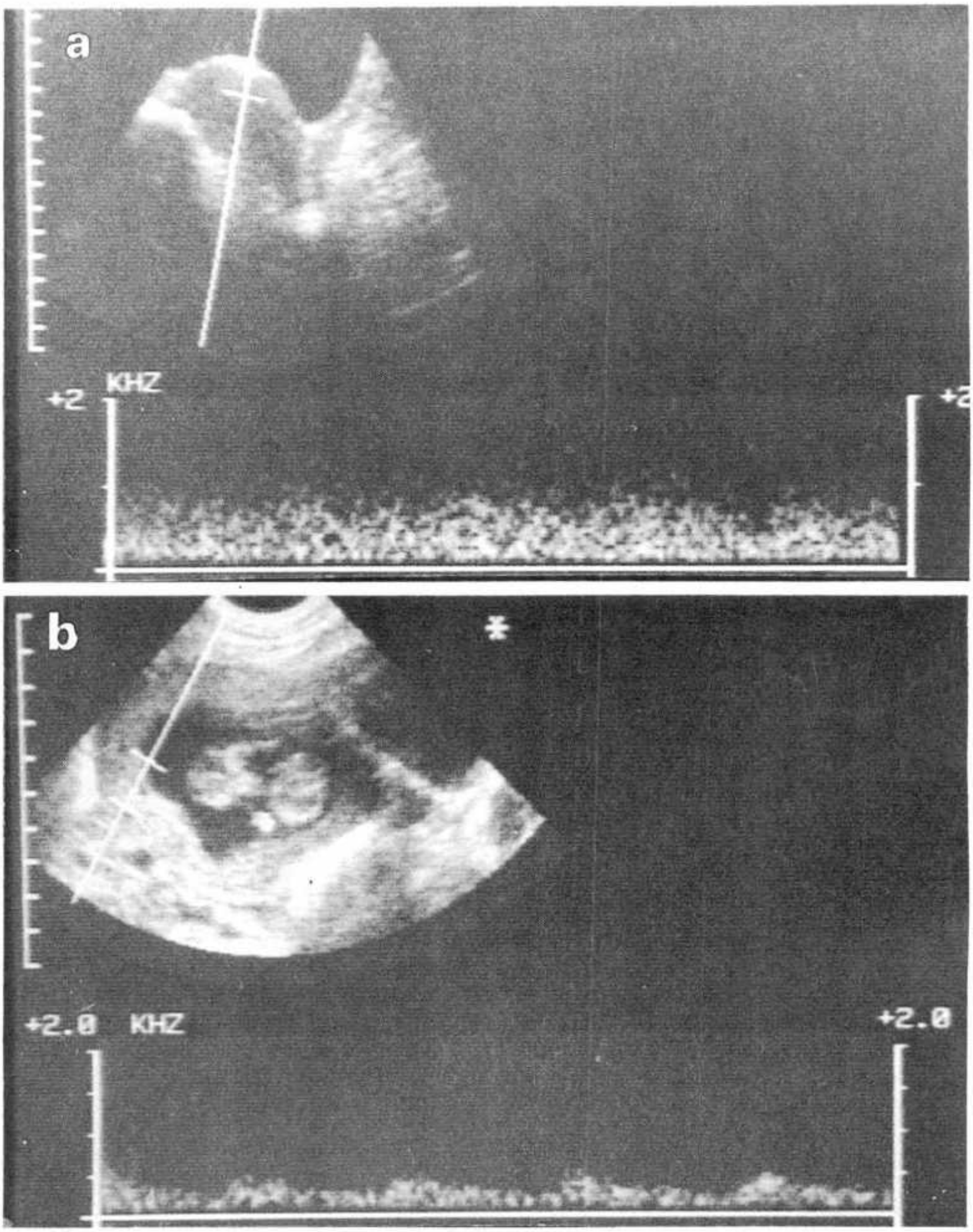

Fig. 3. Myometrial frequency shifted spectra in (a) trophoblastic tumours and (b) early pregnancy.

between the values for the pregnant and non-pregnant subjects ($P<0{\cdot}001$).

Myometrial frequency shifted spectra

Frequency shifted spectra were easily detected throughout the myometrium in 35 of the women with trophoblastic disease. These were of high intensity and could be localized or diffuse (Fig. 3a). They were strikingly different from those seen in the other two groups. Isolated frequency shifted signals of low intensity could be occasionally detected at the lateral borders of the non-pregnant uterus but none were returned from the myometrial substance. Similar signals were found at the borders of the myometrium in pregnancy together with some localized pulsatile waveforms returned from the placental bed (Fig. 3b).

Discussion

The results indicate that the uterine circulation in women with trophoblastic tumours requiring chemotherapy has a very low impedence to flow and is markedly different from that found in the non-pregnant state (Long *et al.* 1989). Although the PI of the uterine artery in pregnancy was lower, the myometrial signals were not as diffuse or of such a high intensity. This suggests that the trophoblast in invasive mole and choriocarcinoma has a greater capacity to form large low resistance channels within the myometrium than in a normal pregnancy. Previous studies using pelvic arteriography in patients with invasive mole or choriocarcinoma have demonstrated the presence of rapidly filling channels within the uterus (Borrell & Fernstrom, 1958). However, Brewis & Bagshawe (1968) showed this to be of little value in the assessment of the response of the tumour to chemotherapy. Doppler ultrasound provides an assessment of the physiological state of the circulation (Gosling 1976) and can be more useful than arteriography. We have shown that trophoblastic tumours requiring chemotherapy have a characteristic Doppler ultrasound profile. Therefore, this technique may be useful in the initial investigation of patients presenting with persistent trophoblastic diseases. Further studies are in progress to elucidate its role as a prognostic indicator of response to cytotoxic chemotherapy.

Acknowledgments

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Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia

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Summary. In 20 women with menorrhagia (>80 ml blood loss per menstrual period) a levonorgestrel-releasing intrauterine device (Lng-IUCD) was inserted. Menstrual blood loss (MBL) was measured in two consecutive cycles before the device was inserted and after 3, 6 and 12 months of use. MBL was significantly reduced after 3 months (86%) and after 12 months the reduction was 97%. There was a significant increase ($P<0{\cdot}001$) in serum ferritin during the first year of Lng-IUCD use. The Lng-IUCD seems to be an important alternative to oral medication and to hysterectomy in the treatment of menorrhagia.

Menstrual blood loss is the most common cause of iron deficiency in healthy fertile women. Heavy menstrual bleeding is seldom overlooked but a moderate increase in menstrual blood loss, sufficient to create a negative iron balance, may escape notice. Women with unexplained iron deficiency should be questioned carefully about their periods, but subjective impressions have been shown to bear little relation to measured blood loss (Chimbira *et al.* 1980, Fraser *et al* 1981) and it is important to use an objective method to assess a treatment for menorrhagia. (Hallberg & Nilsson 1964; Newton *et al.* 1977).

The normal menstrual blood loss (MBL) is estimated to be between 20 and 60 ml and iron deficiency anaemia is more frequent if the blood loss exceeds this amount. Most women who lose ⩾80 ml each period become iron deficient and a blood loss above this limit has been defined as menorrhagia (Hallberg *et al.* 1966).

Serum ferritin is a very sensitive non-invasive indicator of tissue iron stores and can be used to detect iron deficiency (Jacobs *et al.* 1972).

Treatment of menorrhagia by the intrauterine release of progesterone from the intrauterine contraceptive device (IUCD), Progestasert, has been shown to reduce MBL by 65% after 12 months of use (Bergkvist & Rybo 1983). Levonorgestrel is not metabolized by the endometrium as rapidly as progesterone (Nilsson *et al.* 1978), and the intrauterine release of levonorgestrel has been shown to reduce MBL (Nilsson 1977) and to increase the concentration of serum ferritin (Heikkila *et al.* 1982) in women with normal menstrual loss.

With these findings in mind, we wanted to determine to what extent the intrauterine release of levonorgestrel would reduce blood loss in women with menorrhagia and if the treatment could increase the body iron stores.

Subjects and methods

The levonorgestrel-releasing intrauterine device (Lng-IUCD) is manufactured by Huhtamäki Oy Leiras, Turku, Finland. The device has the same T-shaped polyethylene skeleton as the Nova-T and the steroid is homogeneously dispersed in a polydimethylsiloxane reservoir covered by a rate-limiting membrane on the vertical arm of

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the device. The total amount of levonorgestrel in the IUCD is 46 mg and the release rate is 20 µg/day. The effective life-span of the Lng-IUCD is estimated at 5 years (Nilsson *et al.* 1977).

The study was performed on healthy parous women who visited our out-patient clinic because of heavy menstrual bleeding and who were not planning pregnancy. Inclusion criteria were: (i) age ≤45 years; (ii) regular periods, no intermenstrual bleedings or spottings; (iii) no pregnancy, no use of contraceptive pills or IUCD during the last 2 months; (iv) normal sized or only slightly enlarged uterus and no sign of pelvic pathology; (v) MBL≥80 ml per period during two consecutive cycles.

The study included 20 women with a mean age of 38 years (range 31–45 years). Their mean parity was 2 (range 1–4).' Five women had one child, eight had two, six had three and one had four children. The median uterine length measured before the IUCD insertion was 8 cm (range 7–9 cm).

One woman was excluded from the study because of expulsion of the Lng-IUCD during the first period after insertion. She was 41 years old, para 3 and her MBL was 550 and 449 ml before insertion. A hysterectomy was later performed, the endometrium was normal at histopathological examination, but there were submucous fibroids.

In two women the Lng-IUCD was removed before the 6-month follow-up because of intermenstrual bleeding. One of these women had a hysterectomy; the endometrium was normal but she had submucous fibroids. One woman had the Lng-IUCD removed after 10 months because of acne, weight-gain (2·5 kg), mood changes and intermenstrual spotting.

Menstrual blood loss was measured as described by Hallberg and Nilsson (1964) and modified by Newton *et al.* (1977). The importance of collecting all menstrual blood was explained to the women and they were told to place a fresh tampon in the vagina before passing urine or emptying the bowel.

Serum ferritin was used to detect iron deficiency. The concentration of ferritin in serum is proportional to total iron stores and to the amount of mobilizable iron (Jacobs *et al.* 1972). Ferritin was measured using the double antibody-polyethylenglycol radioimmunoassay described by Lundberg *et al.* (1984).

For the statistical calculations Wilcoxon matched pairs test was used.

Design of the study

The women were informed about the details of the study and gave their written consent. All women were asked not to take iron, anti-fibrinolytic drugs or salicylates during the study. MBL was measured during two consecutive periods before the IUCD insertion and then after 3, 6 and 12 months. The haemoglobin concentration was measured each time the MBL was measured. Serum ferritin was measured before the insertion and after 6 and 12 months.

The study was approved by the local ethics committee.

Results

The reduction in menstrual blood loss after the insertion of the Lng-IUCD is shown in Fig. 1. The median MBL during the two consecutive periods before insertion was 176 ml (range 80–381 ml). Three months after insertion the MBL was 24 ml (range 0–145 ml), a difference of 152 ml, corresponding to an 86% reduction in MBL. This reduction is statistically significant ($P<0{\cdot}001$). The median blood loss 6 and 12 months after IUCD insertion was 15 ml (range 0–119 ml) and 5 ml (range 0–33 ml).

Intermenstrual bleeding or spotting was reported by most women during the first three cycles after insertion but the frequency diminished gradually. The amount of blood loss as spotting was estimated by the women to be very small and was not measured.

Table 1 shows the serum ferritin and the haemoglobin concentration before and after Lng-IUCD insertion. After 12 months the mean serum ferritin concentration had increased significantly ($P<0{\cdot}001$). Only those women who came for the 6 or 12 months follow-up were included in the investigation of ferritin levels. At the 6 months follow-up there were three missing data. Seven women had subnormal values (<11 µg/l) on entering the study, and all except one had normal values after 12 months. The mean haemoglobin concentration was significantly increased after 6 and 12 months ($P<0{\cdot}01$). Figure 2 shows the serum ferritin values during the study in 13 women who had ferritin determined before Lng-IUCD insertion and after 6 and 12 months of use. All but one woman had higher serum ferritin values at the 12 months follow-up compared to the pre-insertion values.

Initially 14 women reported that their heavy

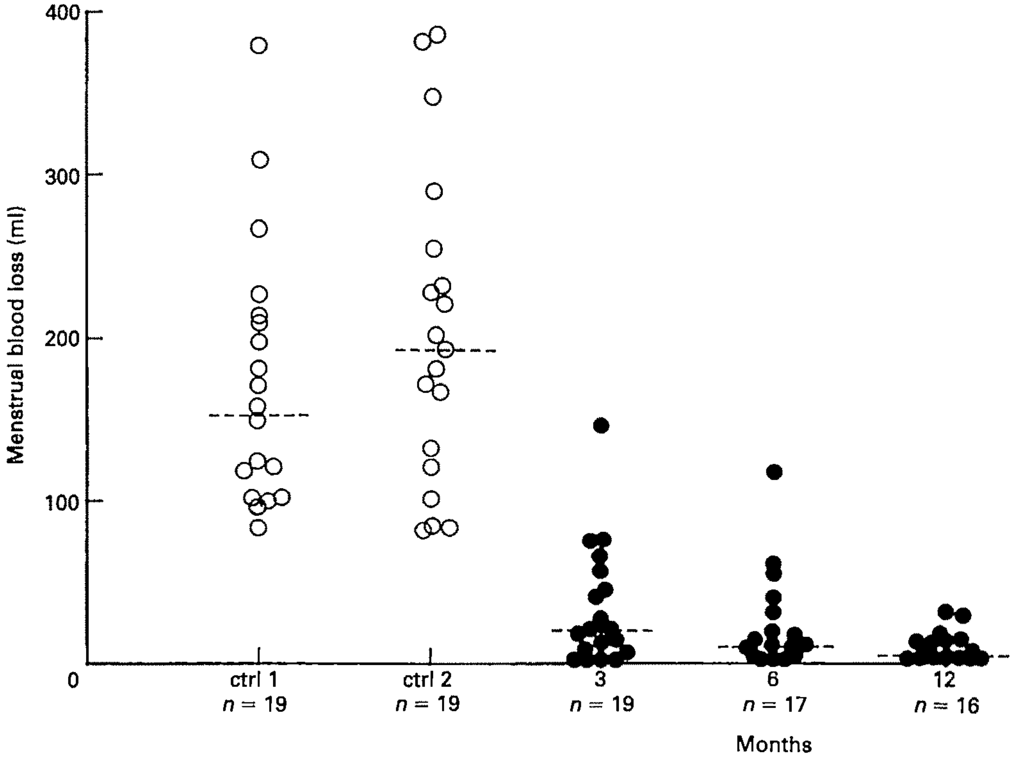

Fig. 1. Menstrual blood loss in menorrhagic women at two control periods (ctrl) before Lng-IUCD insertion and after 3, 6 and 12 months of use. All individual values are indicated, and median values are marked

blood loss more or less restricted their social life. Some felt unable to leave their home when they were bleeding heavily and had to stay home from work 1 or 2 days each period. None had these problems after the insertion of the Lng-IUCD, which thus improved the quality of their life.

Discussion

Menorrhagia, defined as menstrual blood loss exceeding 80 ml per period, is known to be correlated with a significantly increased risk of developing iron deficiency (Hallberg *et al.* 1966). As there can be a variation in blood loss from period to period, two consecutive periods were measured, and the woman was included into the study only if the blood loss exceeded 80 ml in each period.

In the present study the haemoglobin concentration before Lng-IUCD insertion was within normal ranges (120–140 g/l) in all but four women. Many of the women had been treated with antifibrinolytic drugs with or without iron except for the last 2 months before entering the

Table 1. Concentration of haemoglobin and serum ferritin in menorrhagic women before Lng-IUCD insertion and after 3, 6 and 12 months of use.

	Time after IUCD insertion (months)			
	Before insertion	3	6	12
Haemoglobin (g/l)	128 (7·7) (n=19)	132 (9) (n=19)	138 (7)* (n=17)	139 (12)* (n=16)
Ferritin (µg/l)	15.3 (7) (n=17)	not done	17·6 (12·3) (n=14)	28·8 (13)† (n=16)

Results are mean (SD) values, n=number of women Comparison with values before IUCD insertion *P<0·01, †P<0·001.

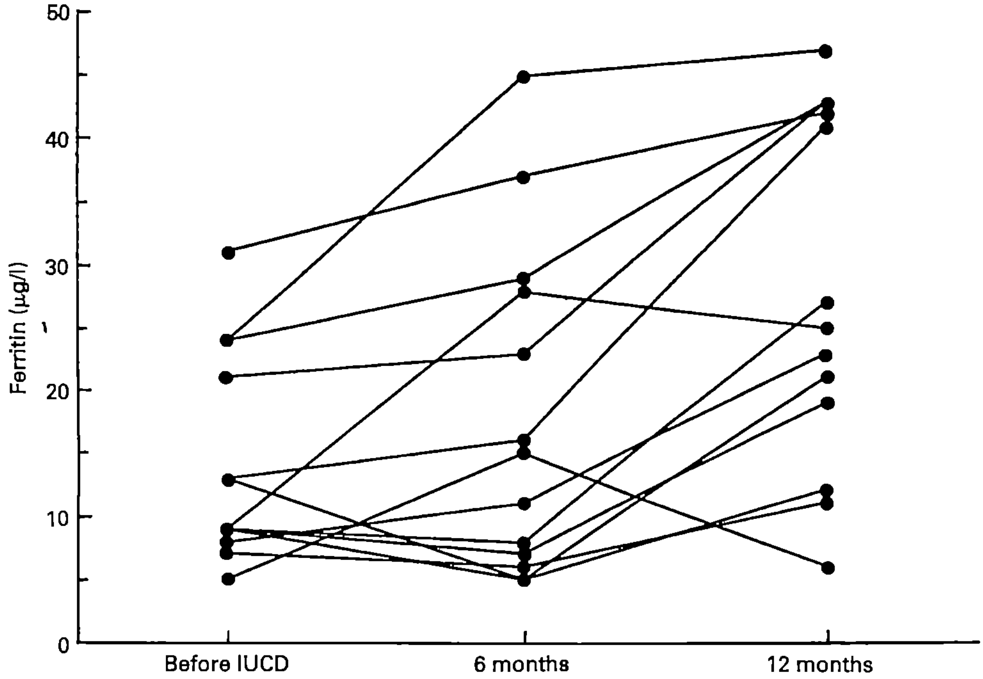

Fig. 2. Changes in serum ferritin levels in 13 menorrhagic women before Lng-IUCD insertion and after 6 and 12 months of use. Only women whose serum ferritin was determined at all these occasions are included in the figure.

study. This treatment may have prevented them from having subnormal haemoglobin-values. However, seven of the 19 women had serum ferritin concentrations below the normal range (11–120 µg/l) indicating depleted iron stores before the Lng-IUCD insertion. In all but one woman the serum ferritin had increased after 12 months of Lng-IUCD use, suggesting that when the MBL decreased the amount of storage iron returned to normal.

The women included in this study had a normal sized or slightly enlarged uterus, no signs of pelvic pathology at bimanual examination and no intermenstrual bleeding. Menorrhagia, without other complaints, is usually not associated with endometrial pathology and consequently the endometrium was not investigated (Rybo 1983).

The use of intrauterine progesterone has been shown to be effective in the treatment of menorrhagia (Bergkvist & Rybo 1983) and is associated with the changes in the endometrium caused by progesterone (Hagenfeldt *et al.* 1977). Levonorgestrel is not metabolized by the endometrium as rapidly as progesterone and has a more uniform and profound local effect (Nilsson *et al.* 1978). The Lng-IUCD was shown to reduce MBL by 63% after 3 months of use in women with normal periods (Nilsson 1977).

The present study shows that a Lng-IUCD is more effective in the treatment of menorrhagia than a progesterone-releasing IUCD.

The use of progesterone in an IUCD (Progestasert) in menorrhagic women decreased the MBL by 65% after 12 months of use compared with pretreatment periods (Bergkvist & Rybo 1983). Three months of use of the Lng-IUCD reduced MBL by 86% and the reduction at 12 months was 97%. It is known (Luukkainen *et al.* 1987) that the Lng-IUCD can cause amenorrea in some women. This occurred in the present study. Four of the women in our study had no bleeding in their third cycle but scanty bleeding could occur at the expected time of menstruation in later cycles. Seven women had no bleeding at 12 months after insertion.

There are other treatments of menorrhagia. Oral contraceptives (Nilsson and Solvell 1967) and antifibrinolytic agents (Nilsson & Rybo 1971) have been shown to reduce MBL by about 50%.

Inhibitors of prostaglandin synthesis can also reduce MBL in women with menorrhagia. Mefenamic acid has been shown to reduce MBL by 30% (Fraser *et al.* 1981) and naproxen by 24% (Rybo *et al.* 1981). Hall *et al.* (1987) reported that naproxen and mefenamic acid in higher doses reduced MBL by 46% and 47%, respectively.

Daily treatment with danazol reduced MBL by 86% in women suffering from menorrhagia (Chimbira *et al.* 1980).

Hysterectomy is sometimes necessary to cure women with menorrhagia, but may be inappropriate in younger women and unnecessary in women nearing the menopause.

The greatest disadvantage of the use of the Lng-IUCD is intermenstrual bleeding and spotting and these problems were frequent during the first months of use. In two women the intermenstrual bleeding was unacceptable and the device was removed. One woman had intermenstrual spottings in combination with hormonal side effects and the treatment was discontinued. Overall the frequency of side effects was acceptably low and the Lng-IUCD proved to be a most effective treatment for menorrhagia and, in many of the women, an alternative to hysterectomy.

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Accuracy of ultrasound measurements of female pelvic organs

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Summary. Uterine size, endometrial thickness and ovarian volume were measured ultrasonically and the results compared with caliper measurements made shortly afterwards at the time of total hysterectomy and bilateral salpingo-oophorectomy. The results establish the validity of ultrasound measurements. Histological studies also confirmed the diagnosis made with ultrasound of polycystic ovaries in women complaining of pain due to pelvic congestion.

Assessment of the size of the uterus and ovaries by vaginal examination is, at best, only a rough guide as to whether or not these organs are larger than normal. It does not provide reliable longitudinal data on changes in size or on any pathology lying within a uterus or ovary of apparently normal size. Ultrasound imaging has the potential to overcome all the drawbacks of the vaginal examination as well as giving information on changes in endometrial thickness but this method needs to be assessed before clinicians can use it with confidence. In addition, the finding of polycystic ovaries (PCO) on ultrasound scanning in normal women (Polson *et al.* 1988) needs to be confirmed histologically.

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Patients and methods

Forty-seven premenopausal women were recruited to the study over a 9-month period. Eight were excluded because of difficulty in imaging their pelvic organs due to large fibroids in seven and obesity in one. One patient declined surgery. The remaining 38 women had detailed transabdominal pelvic ultrasound scanning within 24 h of total abdominal hysterectomy and bilateral salpingo-oophorectomy for pelvic pain due to congestion in 17 or total abdominal hysterectomy with ovarian conservation for other indications in the other 21. Pelvic congestion was diagnosed by venography as described by Beard *et al.* (1984).

Pelvic ultrasonography

All patients were scanned on the day before operation by one of two operators (C.F. or T.R.) An Acuson 128 ultrasound machine with a 3·5 MHz sector probe was used. The patient was scanned in the supine position with a full bladder. The longitudinal and anteroposterior dimensions of the uterus were taken from a single image of the longest uterine section. The longitudinal measurement was taken from the highest fundal point in the midline to the corresponding midline cervical point. The anteroposterior measurement was taken at 90° to this plane, at the widest fundal dimension. In the

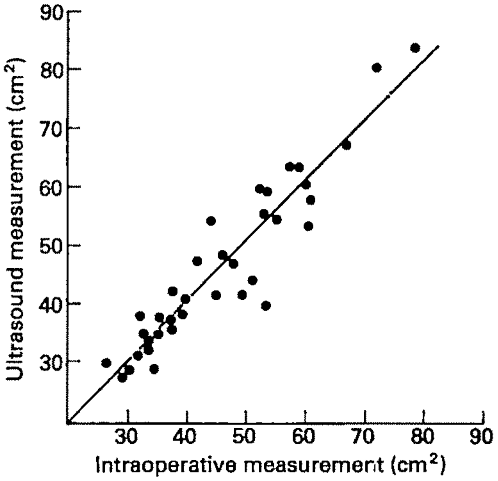

Fig. 1. Uterine cross sectional area (cm^2). Comparison of ultrasound and intraoperative measurements in 38 patients.

case of a retroverted uterus, the longitudinal measurement was traced using a linear facility of the equipment from the same points as described above. Endometrial thickness was measured in a similar manner with reference to the proximal and distal interfaces between echoic and hyperechoic layers of the endometrium (Fleischer *et al.* 1986). All measurements were made using digital calipers. The ovaries were measured in three planes and their volumes calculated using the simplified formula for a prolate ellipse (½ × length × width × thickness; Sample *et al.* 1977). It is recognized that an estimate, made in this way, of an irregular sphere such as the ovary, is bound to be, at best, an estimate of the true volume. In addition measurement by ultrasound of an ovary on the left is often made more difficult by an overlying sigmoid colon, particularly if it contains a lot of gas. Finally the presence, dimensions and distribution of ovarian follicles were assessed. When the ovarian volume was 9 cm^3, and when peripheral distribution of follicles was noted an ultrasound diagnosis of PCO was made. Some patients also had increased echogenicity of the ovarian stroma and this was also used as a pointer to the ultrasound diagnosis of PCO.

Caliper measurements

Geometric calipers were used to measure the dimensions (± 1 mm) of the uterus and ovaries shortly after their removal. The uterus was measured along its longitudinal axis (uterine length) together with the anteroposterior diameter at the fundus (uterine depth). The uterine area (length × depth) was thereby calculated (Parisi *et al.* 1982). The uterus was then opened anteriorly in a longitudinal fashion and the endometrial thickness was recorded. The ovarian volumes were calculated in the same manner as was used for ultrasound. When the ovaries were conserved, the same measurements in three planes as described previously were used *in situ* in the abdomen at operation.

Histological examination

The ovaries were examined by one histopathologist (M.A.) who was unaware of the ultrasound or laparoscopic findings. The ovaries were fixed in Bouin's fluid and blocks were taken centrally, along the long axis of the ovary with sections cut at 4 μm. These were then mounted, stained with haematoxylin and eosin and studied with particular reference to the size, number and distribution of cystic follicles.

Statistical methods

The results of the two methods of measuring the pelvic organs are displayed graphically with the line of identity. The mean differences between the two methods of measurement are given with their 95% ranges (mean ± 2SD) and the correlation between the differences and mean of each pair of readings is used to assess bias (Altman and Bland 1983).

Table 1. Difference between ultrasound and intraoperative measurement

	Mean	SD	95% range	*n*
Uterine cross-sectional area (cm^2)	−0·83	4·93	−10·50 to 11·33	38
Endometrial thickness (mm)	0·63	2·01	− 3·30 to 4·56	38
Ovarian volume (cm^3)				
Right	0·06	3·27	− 6·34 to 6·47	36
Left	−0·02	2·06	− 4·06 to 4·01	36

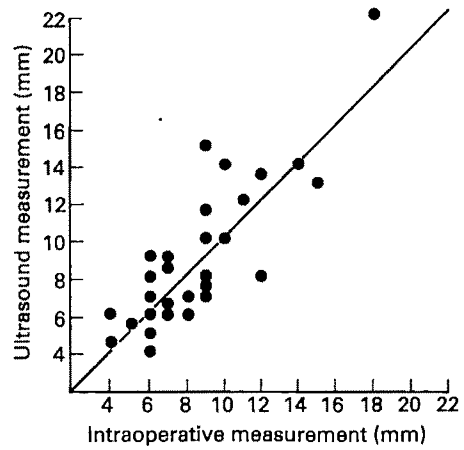

Fig. 2. Endometrial thickness (mm). Comparison of ultrasound and intraoperative measurements in 38 patients

Results

Uterine cross-sectional area

A comparison between uterine cross-sectional area as determined by ultrasound and direct measurement is shown in Fig. 1. The mean difference between measurements was −0·83 cm^2 (95% range −10·50 to 11·33 cm^2) which is not significantly different from zero (Table 1). There was no significant correlation between the differences and means of pairs of measurement ($r = -0{\cdot}26$).

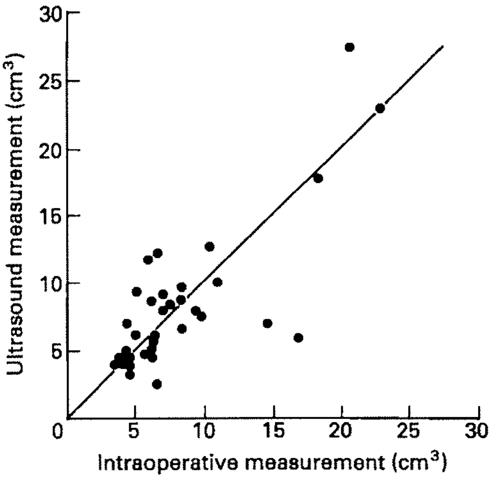

Fig. 3. Volume of right ovary (cm^3). Comparison of ultrasound and intraoperative measurements in 36 patients

Endometrial thickness

The relation between the thickness of the endometrium as measured by ultrasound compared with direct measurements after hysterectomy is shown in Fig 2. The mean difference between measurements was 0·63 mm (95% range −3·30 to 4·56 mm) which is not significantly different from zero (Table 1). There was no significant correlation between the differences and means of pairs of measurements ($r = 0{\cdot}29$).

Ovarian volume

Figures 3 and 4 show the relation between ovarian volumes as measured by ultrasound and by direct caliper measurement for the right and left ovary. There was no significant correlation between differences and means of measurements for the volume of the right ovary ($r = 0{\cdot}14$), but those of the left ovary showed a significant correlation between the differences and the means ($r = 0{\cdot}55$, $P < 0.001$). The effect of this can be seen in Fig. 4 where the ultrasound measurement is noticeably higher than the intraoperative measurement for the larger ovaries. This relation remained significant even after logarithmic transformation. The mean and 95% ranges were 0·6 cm^3 (−6·34 to 6·47 cm^3) and −0·02 cm^2 (−4·06 to 4·01 cm^3) for volumes of the right and left ovaries, respectively, neither of which is significantly different from zero.

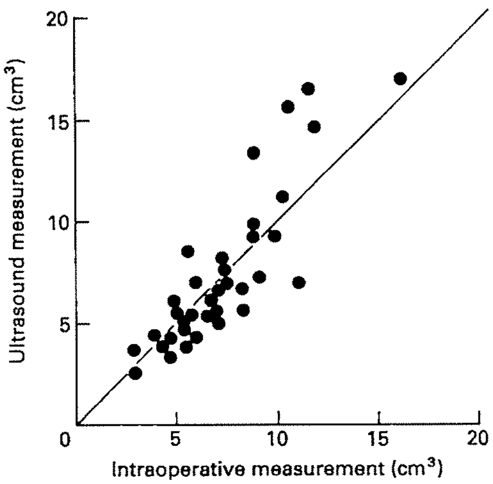

Fig. 4. Volume of left ovary (cm^3). Comparison of ultrasound and intraoperative measurements in 36 women.

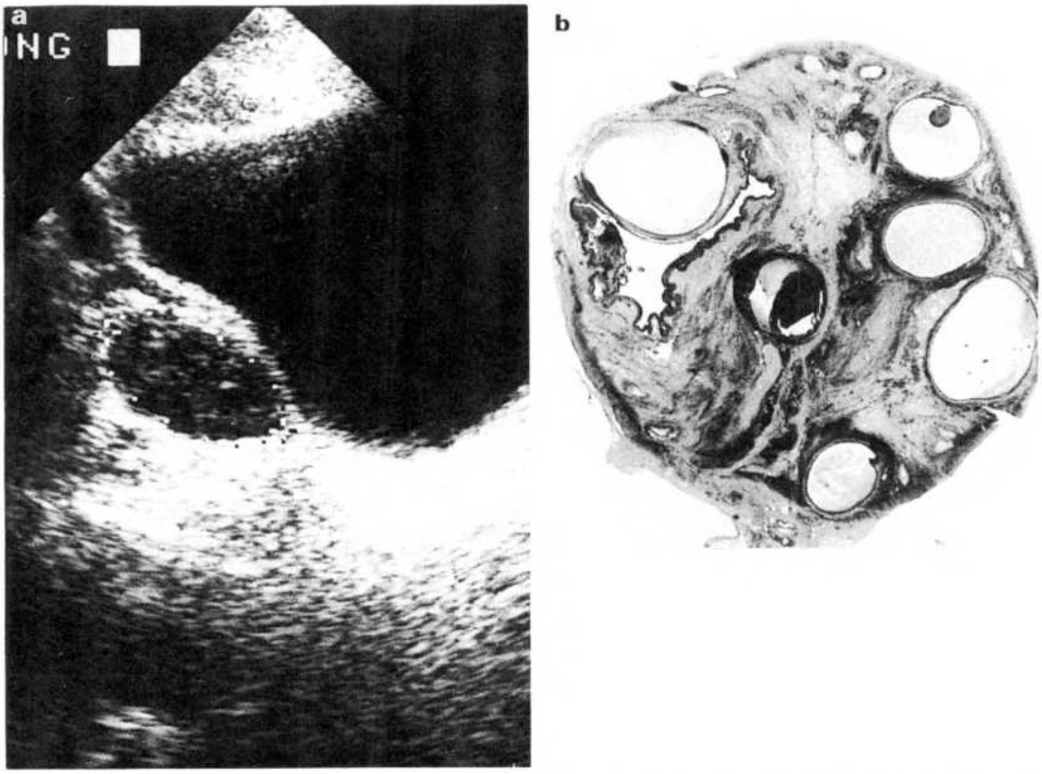

Fig. 5a. Ultrasonograph of cystic ovary. **Fig. 5b.** Histological section of a transverse slice through the cystic ovary shown in Figure 5a. There are six cystic follicles five of which are located in the subcortical region. Smaller, atretic follicles are also apparent. (Haematoxylin and eosin × 3.7).

Cystic ovaries

Figure 5a shows an ultrasound scan of an ovary which is compared with a histological section of the same ovary shown in Fig. 5b. An ultrasound diagnosis of PCO was made in 14 women with pelvic congestion. The 28 ovaries from these women all had multiple cystic follicles on histological examination with a mean of seven cysts per ovary, mainly situated peripherally. The ovaries removed from the remaining three women with pelvic pain but without an ultrasound diagnosis of PCO did not contain multiple cystic follicles. There was therefore perfect correlation between an ultrasound diagnosis of a cystic ovary and the histological findings. Some degree of stromal hyperplasia was found in 61% of the cystic ovaries.

Discussion

Previous studies have shown close agreement between ultrasound appearances and ovarian endocrine profiles (Parisi *et al.* 1984) and with the histological features of normal and abnormal endometrium (Fleischer *et al.* 1986). El Tabbakh *et al.* (1986) showed agreement between ultrasound measurements of the ovaries and appearances at laparascopy although the numbers were small and no caliper or volume measurements of the ovaries were made. The present study is the first to compare the absolute dimensions of the pelvic organs with ultrasound measurements and shows a high level of agreement between the two techniques of measurement. No significant consistent error of difference between readings was observed in any of the structures measured. However, although no significant bias was observed in the measurement of uterine area or endometrial thickness, the results for ovarian volume were less convincing, and there was significant bias for those of the left ovary.

There have been many ultrasound studies of polycystic ovaries and the features are well described. Some workers have attempted to define different subgroups of polycystic ovaries based on ultrasound appearances (Takahashi *et* *al.* 1988). Our study has shown that multiple cysts in ovaries can be detected reliably by ultrasound but until the in-depth study of the histology of these ovaries has been completed it is not possible to be sure whether or not these changes are similar to classical polycystic ovaries. The ultrasound image of multiple cysts of variable size corresponds exactly to the polycystic pattern of follicles located predominantly beneath the ovarian cortex observed on histological section.

Polson *et al.* 1988), in an ultrasound study of the general population, reported a 23% prevalence of PCO. In a similar study of women with pelvic pain due to congestion, 56% of affected women had an ultrasound diagnosis of PCO (Adams *et al.* 1986). This relatively high prevalence amongst women of reproductive age suggests that while ovaries quite commonly undergo cystic or polycystic change for reasons as yet undetermined, it is commoner among women with pelvic congestion. The functional significance of ultrasound PCO, and whether these changes can revert to normal, still has to be determined. The demonstration that ultrasound can provide accurate measurements of pelvic organs suggests that in the future such measurements will be used increasingly to complement vaginal examination.

Acknowledgments

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Aortic compression by the uterus: identification with the Finapres digital arterial pressure instrument

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Summary. Aortic compression by the uterus at term was diagnosed when reversible reductions in toe pulse pressure, measured using a Finapres digital blood pressure instrument, were found in the absence of systemic hypotension, monitored by a second instrument with the cuff on a finger. Aortic compression was found in the left or right pelvic tilt positions in 14 of 32 women, sometimes with up to 34° of tilt, and was relieved by increasing the amount of tilt, except in a twin pregnancy where compression became more severe as left pelvic tilt was increased from 13° to 28°. Compression was also found in two women in the semi-recumbent position. Factors associated with an increased likelihood of aortic compression were non-engagement of the fetal head, occipito-posterior position of the fetal head, and cervical dilatation less than 5 cm.

Supine aortic compression by the term uterus was demonstrated by Bieniarz *et al.* (1966) using invasive measurements of systemic arterial pressure from the femoral and brachial arteries. It was found to be exacerbated by uterine contractions (Bieniarz *et al.* 1966, Abitbol 1977) and reduced by the use of left pelvic tilt (Eckstein & Marx 1974). Goodlin (1971) found a frequency of up to 37% in the supine position during labour.

The Finapres (Ohmeda, Hatfield, Herts.) is a new instrument which measures digital arterial pressure continuously and non-invasively, using the Penaz principle (Penaz 1973). We used the device, with the cuff placed on a toe, to indicate aortic compression and studied the effectiveness of the pelvic tilt position to relieve the compression.

Subjects and methods

Thirty unselected women with cephalic singleton pregnancies at term were studied. Three were having Braxton Hicks contractions and the others were in labour, ranging from early labour to late first stage. Twenty were in spontaneous labour, seven had been induced with prostaglandin pessaries. In addition, one woman with a twin pregnancy and one with a breech presentation were studied, both in established labour.

The cuff of a Finapres instrument was placed on the right first toe. A photoelectric plethysmograph (pulse monitor) was placed on an adjacent toe. The cuff of a second Finapres instrument was placed on the right middle finger. Fetal heart rate (FHR) and uterine contractions were monitored with external transducers, or with a fetal scalp electrode and intrauterine pressure catheter when clinically

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indicated. Engagement of the fetal head was assessed by abdominal palpation, and the position of the fetal head and cervical dilatation by vaginal examination.

The Finapres has been studied for accuracy when used on the finger (van Egmond *et al.* 1985) but not on the toe, and therefore pressures in the toe were not calibrated for absolute values. However, changes in pressure in the toe normally followed changes in finger pressure very well (Fig. 1).

Aortic compression was diagnosed when a reversible reduction in toe pulse pressure (Abitbol 1977) accompanied by a decrease in plethysmographic pulse amplitude (Goodlin 1971, Abitbol 1977) occurred. This usually coincided with uterine contractions (Fig. 2), but was sometimes present with a non-contracted uterus (Fig. 3). The reduction in pulse pressure, indicating severity of aortic compression, was graded as: mild, up to 33% reduction; moderate, 33–50% reduction; severe, >50% reduction during a contraction compared with the pulse pressure just before the contraction. In the case of aortic compression with a non-contracted uterus, the change in pulse pressure was compared to that in the previous position. This grading was described by Abitbol (1977) although he compared the reduction in femoral pulse pressure with a baseline taken in the left lateral position.

After control readings taken in the initial resting position, women were placed with left pelvic tilt using a Crawford wedge under the contralateral hip, and the angle of inclination of the pelvis was measured using a protractor device, with an estimated accuracy of 1–2°. If aortic compression was found, this angle was increased progressively, until the phenomenon disappeared. Twenty-one women were also studied with right pelvic tilt in a similar fashion. The supine position was only studied if the woman was originally in that position, or if it was assumed during the course of a clinical procedure while monitoring was in progress.

The association between aortic compression

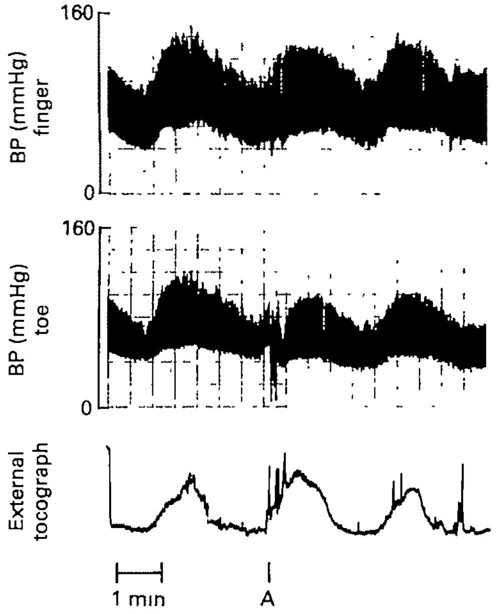

Fig. 1. Arterial pressure fluctuations in the finger and toe during uterine contractions, without evidence of aortic compression Upper trace—blood pressure (BP) (Finapres) recorded from the right middle finger. Middle trace—BP (Finapres), right first toe. Lower trace—external tocograph. (A) Change from sitting to 11° left pelvic tilt position.

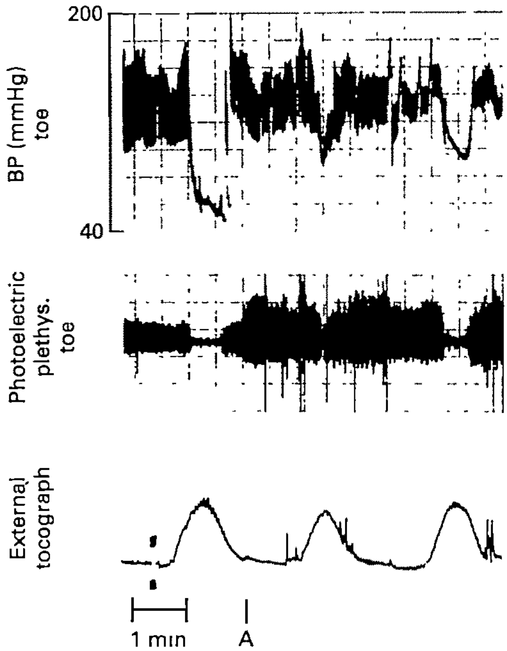

Fig. 2. Intermittent aortic compression with uterine contractions Recording from a subject in the semirecumbent position. Upper trace—arterial BP (Finapres), right first toe. Middle trace—photoelectric plethysmograph (pulse monitor) trace recorded from the right second toe (A—gain increased ×2). Lower trace—external tocograph. Evidence of aortic compression, concurrent with uterine contractions, can be seen in both the BP and plethysmographic recordings.

and FHR was assessed from the cardiotocograph traces which were analysed for FHR decelerations or bradycardia by one author (J.A.D.S). This analysis was 'blind' to any information on maternal position or changes in toe arterial pressure during the recording period.

Statistical analysis was performed using the χ^2 test to investigate the influence of parity, engagement of the fetal head, cervical dilatation, the lateral position of the fetal spine in the uterus (maternal left or right), and the presence of epidural anaesthesia on the frequency of aortic compression in 30 women with singleton cephalic pregnancies.

The study had local ethics committee approval and informed consent was obtained.

Results

The details of the women with singleton cephalic pregnancies are shown in Table 1.

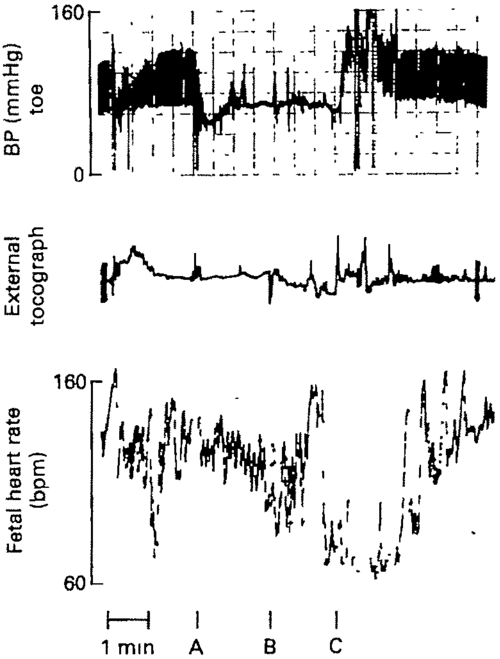

Fig. 3. Aortic compression, non-contracted uterus Upper trace—arterial BP (Finapres), right first toe. Middle trace—external tocograph. Lower trace—fetal heart rate Subject initially in 34° left pelvic tilt position. (A) Subject turned to a 28° right pelvic tilt position. (B) Right pelvic tilt increased to 34°. (C) Subject placed in the left lateral position. Evidence of aortic compression is present at 28° and 34° right pelvic tilt in the absence of uterine contractions, and is associated with severe deceleration of the fetal heart rate There was no change in finger blood pressure during this period.

There was significantly more aortic compression ($P<0{\cdot}05$) if cervical dilatation was <5 cm, and if the fetal head was not engaged. However, all three women with an occipito-posterior position of the fetal head (subjects 16, 22, 28) showed evidence of aortic compression, and when they were excluded from the analysis, non-engagement ceased to be a significant association with aortic compression. Parity, the side of the fetal spine in the uterus, or the presence of an epidural (in the 27 women in labour) had no influence on aortic compression.

Of the 32 women studied, 14 had aortic compression (Table 2); 12 of the 32 in the left pelvic tilt position, 5 of 21 tested in the right pelvic tilt position, and 2 of 4 tested in the supine position. Two women showed aortic compression in the right pelvic tilt position and not the left. Compression was relieved by increasing the degree of pelvic tilt, except in the woman with a twin pregnancy, who showed an increase in aortic compression as the degree of left pelvic tilt was increased from 13° to 28°. Among the whole group, compression was found with up to 34° of tilt and was also present in two women in the semirecumbent position (reclining on a large wedge-shaped cushion in the delivery bed or 'sitting') but was never found in the left or right lateral positions.

In two women severe aortic compression was present with a non-contracted uterus. In the remainder, aortic compression was observed only during uterine contractions.

Fetal bradycardia or late variable decelerations, related to aortic compression, were seen in only four women (Fig. 3), including a similar bradycardia in both twins in response to intermittent aortic compression (subject 31). In one of these women, uterine hyperstimulation was also present.

FHR decelerations were found in one woman in both lateral positions (with no aortic compression) as well as in the supine position with pelvic tilt (when aortic compression was identified), the compression in this case being contributory to some other cause of the decelerations. In two instances there were FHR abnormalities during monitoring, related to maternal position, in the absence of aortic compression: in one woman where fetal bradycardia occurred in the left lateral position and late decelerations in the right lateral position there was a nuchal cord at caesarean delivery, and in the other, fetal bradycardia occurred in the right lateral and both pelvic tilt positions, but a cause was not identified.

Discussion

There were sometimes large differences in both absolute pressure and pulse pressure between the Finapres on the toe and that on the finger, probably because a cuff designed for the finger was used on the toe. We therefore did not use absolute pressure values to indicate aortic compression, but relied on reversible changes in toe pulse pressure with uterine contractions or position change (Figs. 2 & 3). This might have led to aortic compression being missed in some cases.

Aortic compression has been detected using measurement of arterial pressure in the leg (Bieniarz *et al.* 1966, Abitbol 1977, Eckstein & Marx 1974), photoelectric plethysmography in the toe (Goodlin 1971, Abitbol 1977), and Doppler ultrasound flow velocity in the dorsalis pedis artery (Janbu 1989). Continuous monitoring can be performed with the photoelectric pulse monitor, but interpretation can be difficult, especially in the absence of conduction block, because of large spontaneous fluctuations in pulse amplitude. The Finapres allows continuous monitoring with identification of severe aortic compression possible on the cathode ray screen of the instrument, and clearly showed some episodes which were not obvious on the plethysmograph trace alone. By confining the diagnosis of aortic compression to reversible decreases of pulse pressure in the toe, rather than a comparison of arterial pressure in the upper and lower limbs (Bieniarz *et al.* 1966), the second Finapres instrument on the finger is not necessary for clinical monitoring of aortic compression. The infrequency of diagnosis of mild aortic compression may reflect the difficulty in identification of small reductions of pulse pressure among the normal continuous fluctuations of arterial pressure, leading to false negatives. However, this may not be clinically important since mild

Table 1. Details of singleton cephalic pregnancies used for analysis of factors predisposing to aortic compression

Subject no	Antenatal/ labour	Parity	Engagement of fetal head	Cervical dilatation (cm)	Side of fetal spine	Epidural present	Aortic compression present
1	L	0	NE	2	R	N	Y
2	AN	2	E	0	R	—	Y
3	AN	1	NE	0	R	—	N
4	L	0	NE	4	L	N	N
5	L	1	E	2	L	N	N
6	AN	0	NE	0	R	—	N
7	L	0	E	8	L	Y	N
8	L	1	NE	2	L	N	Y
9	L	0	E	2	L	Y	Y
10	L	0	E	2	L	Y	Y
11	L	0	E	8	R	Y	N
12	L	0	NE	0	L	N	N
13	L	0	NE	5	L	Y	N
14	L	1	E	5	L	Y	N
15	L	0	E	4	R	Y	N
16	L	2	NE	1	L	N	Y
17	L	0	E	4	L	Y	N
18	L	0	NE	2	R	Y	Y
19	L	2	E	5	R	Y	N
20	L	1	NE	0	R	N	Y
21	L	1	NE	2	R	Y	Y
22	L	0	NE	4	R	Y	Y
23	L	0	E	2	R	Y	N
24	L	0	E	5	R	N	N
25	L	0	E	3	R	N	N
26	L	0	E	5	L	Y	N
27	L	0	E	4	L	Y	N
28	L	0	NE	5	R	Y	Y
29	L	0	E	4	L	Y	Y
30	L	0	E	8	L	Y	N

compression is less likely to be a cause of a physiologically important decrease in utero-placental blood flow.

Aortic compression with a non-contracted uterus has been shown to be decreased in severity in the left pelvic tilt position when compared to the supine position (Eckstein & Marx 1974). However, we found a 7% frequency of severe aortic compression present with a non-contracted uterus, and a 40% overall frequency, with left pelvic tilt in women with singleton cephalic pregnancies. These percentages are similar to the figures for the supine position noted by Abitbol *et al.* (1986) (8% moderate or severe aortic compression present in the absence of uterine contractions) and Goodlin (1971) (up to 37% during labour). We found aortic compression even with 34° of pelvic tilt, which supports the use of the lateral position for obstetric procedures during labour. It was also found in the semirecumbent position, which has not previously been identified as a position at risk of aortic compression.

Abitbol (1977) showed that severe supine aortic compression was more frequent when the uterus was contracted. Compression might be more frequent and more severe as uterine contractions increase in strength during labour, although most women in our study were monitored with external tocography and thus the strength of contractions was not quantified. The use of intrauterine pressure monitoring might help to elucidate this relation.

We have confirmed the conclusion of Eckstein & Marx (1974) that lesser cervical dilatation was associated with a greater frequency of aortic compression, which may be relieved with descent of the fetal head into the pelvis as the cervix dilates. Although, in agreement with Abitbol (1977), we found that non-engagement of the fetal head was associated with aortic compression, exclusion of these with an occipito-posterior position, all unengaged, abolished this relation. Aortic compression was found in all three women who had an occipito-posterior position of the fetal head. Arterial compression is not painful in itself, but it is interesting to note that the occipito-posterior position is often associated with severe back pain during contractions, said to be caused by pressure on somatic structures. No women with a cervical dilatation of ≥5 cm had aortic compression in the absence of the occipito-posterior position, and conversely, it is likely that women who are having induc-

Table 2. Positions in which aortic compression was identified

			R tilt†				L tilt†			
Subject no	Sitting	R lat	30°	20°	10°	Supine	10°	20°	30°	L lat
1								2	1	0
2	0						3	0		
8		0			3	0	0			
9	0		0		3			3	0	
10			3*				3*	3	0	0
16	3				3	3	3	3		0
18	0						3	3	0	
20	3						3	0		
21	0				0		3	0		
22		0		0	0		3*	3*		0
28						3	2	0		0
29		0			0		2			
31‡	0		0				2		3	
32‡	0			0	3		0			0

0—no aortic compression detected.
1—<33% decrease in toe arterial pulse pressure.
2—33%—50% decrease in toe arterial pulse pressure.
3—>50% decrease in toe arterial pulse pressure.
*—compression present with a non-contracted uterus
† 10° pelvic tilt includes range of angles 6°–15°; 20° includes range 16–25° and 30° tilt includes range 26–35°.
‡ Subject no. 31 had a twin pregnancy with twin 1 cephalic and twin 2 breech, subject no. 32 had a breech presentation

tion of labour and augmentation of contractions with a high fetal head or occipito-posterior position are at the greatest risk.

Because of the interaction between exact maternal position (Abitbol 1977), uterine contractions and fetal position, the severity of aortic compression will vary throughout labour.

Most of the women who had evidence of aortic compression showed no FHR abnormalities, possibly because of unimpaired placental supply from the ovarian arteries, 'placental reserve', and a limited time spent in a position once aortic compression had been identified. Aortic compression as the sole cause of FHR abnormalities was found in three women, and this is understandable in the case of continuous aortic compression persisting even between uterine contractions (Fig. 3). A recent report (Selbing 1988) divided the causes of fetal heart decelerations during active labour into 'placental insufficiency', fetal head compression and umbilical cord compression, and described the use of combined 2-dimensional and Doppler ultrasound to identify the latter. Just as cord compression is normally only diagnosed when a characteristic FHR abnormality is identified; so, without monitoring, aortic compression is only suspected clinically by FHR abnormalities found in the supine position which are relieved by a change in position. Monitoring of toe blood pressure as an index of aortic compression will help to indicate an avoidable cause of 'placental insufficiency' and may allow the correction of maternal position before the decrease in utero-placental blood flow has resulted in FHR changes.

It is concluded that the use of pelvic tilt does not guarantee the absence of aortic compression. Measurement of arterial pressure in the toe using the Finapres instrument provides a method for the study of aortic compression in pregnancy and labour, and could assist the clinical monitoring of obstetric patients.

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Oestrogen and progesterone receptor content as a prognostic factor in advanced epithelial ovarian carcinoma

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Summary. Levels of oestrogen receptor (ER) and progesterone receptor (PgR) in ovarian cancer tissue were examined with regard to their prognostic importance for survival in 179 patients with primary epithelial ovarian cancer stage III or IV in relation to: FIGO-stage, histological type, histological grade, age, ascites, and postoperative residual tumour. Hormone receptor content was determined with the DCC-method, receptor values higher than 9 fmol/mg protein were considered positive. Response to postoperative chemotherapy was significantly correlated with PgR content (80% responders in the group with PgR positive tumours and only 61% responders in the group with PgR negative tumours). A Cox proportional hazards regression model identified histological grade, residual tumour, age and PgR content as independent prognostic factors for survival in advanced epithelial ovarian carcinoma. PgR content had particularly significant prognostic relevance for patients with postoperative residual tumour mass ≤2 cm in diameter. Within this group of patients, those who are PgR positive have a 2-years survival probability of 83% compared with only 51% in the PgR-negative group.

Numerous surveys have shown that oestrogen-receptors (ER) and/or progesterone-receptors (PgR) can be found in patients with malignant epithelial ovarian carcinoma (Jänne *et al.* 1980; Bergqvist *et al.* 1981; Quinn *et al.* 1982; Jones *et al.* 1983; Spona *et al.* 1983; Lantta 1984; Toppila *et al.* 1986). Although the hormone-receptor content of tumour tissue is proven to be an independent prognostic factor for survival in breast carcinoma (Cooke *et al.* 1979; Clark *et al.* 1983; Mason *et al.* 1983) and in endometrial carcinoma (Martin *et al.* 1983; Creasman *et al.* 1985; Liao *et al.* 1986; Sutton *et al.* 1989), surveys on the prognostic value of the hormone-receptor content of malignant ovarian tumours are uncommon and offer only conflicting conclusions obtained from small numbers of patient, usually from heterogeneous groups. Schwartz *et al.* (1986), for example, investigated 101 patients with epithelial ovarian carcinoma in FIGO stages I–IV and concluded that PgR positive patients in stages I

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and II had better prognoses than PgR negative patients. However, of stage III patients with large amounts of postoperative residual tumour after surgery or stage IV patients those who were PgR positive had a significantly lower rate of survival than PgR negative patients.

On the other hand, in a survey of 97 patients with stage III and stage IV epithelial ovarian carcinoma Bizzi *et al.* (1988) showed a significantly higher rate of survival of ER positive patients (ER >9 fmol/mg), but PgR-content was only of marginal significance in terms of survival prognosis.

Yet in a very heterogeneous group of 84 patients, Kauppila *et al.* (1983) found that ER and PgR positive patients had better chances of survival than receptor negative patients.

Other authors yet again, (Teufel *et al.* 1983; Richman *et al.* 1985; Anderl *et al.* 1988) found no connection between hormone-receptor content and survival prognoses for patients with malignant ovarian tumours.

To investigate this issue, we compared retrospectively the prognostic relevance of ER and PgR content to known prognostic factors such as FIGO stage, histological type, histological grade, age, ascites, and size of postoperative residual tumour in patients with primary epithelial ovarian carcinoma in stages III and IV.

Patients and methods

Between December 1982 and December 1988 a total number of 300 patients with primary epithelial ovarian carcinoma in FIGO stage III and IV were treated at or referred to the university hospital of Vienna. In 179 of these patients tumour tissue was examined for hormone receptor content on the occasion of initial surgery. In the remaining 121 patients hormone receptor analysis was not performed because personnel were not available, or because of local organisational problems. The decision to perform hormone receptor analysis was made purely at random and was not influenced by patients' characteristics. All patients whose tumour tissue was examined for hormone receptor content on the occasion of initial surgery were included in this survey. The potential observation time was around 36 months (6–72 months). Patients with borderline carcinoma, or who had been treated previously with cytostatics and those with non epithelial ovarian carcinoma were not included in the study.

Tumour tissue preparation and hormone receptor analysis

Tumour specimens were dissected free of fat and necrotic tissue by our pathologist immediately on receipt and stored in liquid nitrogen, ER and PgR were estimated within 10 days using saturation analysis as reported previously (Spona *et al.* 1979). Briefly, tissue samples weighing approximately 1 g were homogenized deep frozen in a Mikrodismembrator (Braun Melsungen, Melsungen, FRG) for 60 s and 10 vol of TEGD buffer (10 mM Tris, 1 mM EDTA, 30% glycerine, 6 mM dithiothreitol, pH 7·2) was added thereafter to extract the cytosol. The total homogenate was centrifuged at 800 g for 10 min and the supernatant was spun at 105 000 g in a Spinco L2-65B centrifuge (Beckman Instruments, Palo Alto, CA) for 60 min to obtain the cytosol fraction. Cytosol samples (100 µl) were incubated in duplicates in the presence or absence of a 250-fold excess of unlabelled hormone (100 µl) with 100 µl labelled hormone at concentrations of 0·2, 1·0 and 10 nM. After incubation at 0–4°C for 18 h, 0·5 ml of a DCC suspension (0·6% Norit, 0·06% Dextran T-70 in 1 mM Tris, pH 7·2) was added and incubation continued for another 20 min. The tubes were centrifuged at 3000 g for 15 min and the supernatant was transferred to counting vials, 10 ml Instagel (Packard Instruments Inc, Downers Grove, IL) was added and radioactivity was measured on a Packard Scintillation Counter, Tricarb Model 460 CD. Specific binding was calculated by subtracting radioactivity data in a set of tubes with unlabelled hormone from those without non-radioactive steroid. Scatchard plot analysis (Scatchard 1949) or saturation data for the calculation of number of binding sites and affinity constants was performed on a Dec Data System PDP 34/11 (Digital Equipment Corp., Maynard MA).

The assay of ER levels was done with 3H-labelled 17β-oestradiol, specific activity 98 Ci/mmol (Radiochemical Centre, Amersham, UK). Diethylstilboestrol which was used to account for unspecific binding in the ER assay was obtained from Sigma, St Louis, MO. The ligand used for PgR assays was (3H)-R 5020 ((6,7-3H)-17α, 21-dimethyl-19-norpregna-4,9-diene-3,20-dione) at a specific activity of 90 Ci/mmol. Labelled and unlabelled R 5020 was purchased from New England Nuclear, Boston, MA.

Cytosol proteins were measured as described by Lowry *et al.* (1951). Receptor levels >9 fmol/mg protein were classified as receptor positive.

Postoperative treatment comprised cisplatinum-containing polychemotherapy in 152 patients, 134 of them received a sequentially alternating polychemotherapy consisting of Adriamycin (50 mg/m^2 i.v.) on day 1 and cisplatinum (100 mg/m^2 i.v.) on day 2, vincristine (1,4 mg/m^2 i.v.) on day 29 and cyclophosphamide (1500 mg/m^2 i.v.) on day 30, and high-dose methotrexate (500 mg/m^2 i v.) on day 57 plus Leucovorine rescue (3 mg i.m. every 6 h for 36 h) on day 58 to 59. A second cycle of this sequential alternating polychemotherapy was repeated after 4 weeks. The other 18 patients received a combination of Adriamycin (50 mg/m^2 i.v.) and cisplatinum (50 mg/m^2 i.v.) every 4 weeks for a total number of six cycles. In 22 patients cisplatinum-containing therapy was not clinically justified and they were treated with a melphalane monotherapy, the remaining five patients died before they could be treated. The rate of response to postoperative treatment was characterized according to the WHO criteria. Of the 179 women 17 (9·5%) were not assessable for response; five died within one month of the operation, six declined further treatment after the first cycle of chemotherapy and six did not attend for follow-up. Follow-up examinations were performed every 3 months for the first 3 years; every 6 months up to 5 years, and yearly thereafter.

WHO criteria (Serov *et al.* 1973) were used for histology and histologic grading used the criteria of Day *et al.* (1975), highly differentiated tumours being grade 1 and undifferentiated tumours grade 3. The stage was classified in compliance with FIGO criteria in use till 1985.

Statistical methods

Survival time was defined as the period between the date of first surgery and death or the last follow-up. All patients were included in the survival analysis. Survical probabilities were calculated by the method described by Kaplan & Meier (1958). Survival times of patients still alive were censored in June 1989. Differences between groups were tested according to Mantel (1966). Cox proportional hazards regression models (Cox 1972) were used to identify independent prognostic factors from FIGO-stage, histological type, histologic grade, age, ascites, diameter of residual tumour mass, ER and PgR content. Possible interactions of PgR with various prognostic factors were also investigated by Cox's model following Schemper (1988). A confirmed interaction thus indicates that the prognostic role of PgR depends on the level of another factor. Frequencies were compared using the usual χ^2 test comparing observed and expected numbers of events. All *P*-values are results of two-sided tests.

Results

Between December 1982 and December 1988, 179 patients qualified for this study. The potential observation time was around 36 months (6–72 months). The ER and PgR content of tumour tissue is listed in Table 1.

No association was found between ER content and tumour characteristics. In contrast, the percentage of PgR positive tumours was significantly higher in younger patients (≤49 years) and in those who responded to chemotherapy (Table 2). Whereas 43 out of 54 PgR positive patients (80%) responded to chemotherapy, this was true only for 66 out of 108 PgR negative patients (61%).

Univariate analysis showed highly significant variations in survival in relation to FIGO stage, histologic grade, age, ascites, residual tumour and PgR content (Table 3). ER content and histological type, comparing serous carcinoma with all other histological sub-groups, were of marginal significance

In the multivariate analysis, the same variables were independently prognostic apart from stage and ascites. The omission of stage is easily explained by the large correlation between stage and the size of the residual tumour.

The following four single factors were found to be the most relevant individual, highly significant prognostic factors for survival: (i) histological grade with a 2·16-times higher risk of dying from ovarian cancer for undifferentiated tumours compared with well or moderately well differentiated tumours; (ii) the age-factor with a risk 1·94-times higher for patients >49 years compared with <50 years of age; (iii) size of residual tumour with a 1·9-times higher risk for tumours >2 cm in diameter compared with ≤2 cm and (iv) PgR content, with a risk 0·54-times small for PgR positive tumours.

By means of interaction tests within the Cox model (Schemper 1988) we examined possible

Table 1. Oestrogen receptor (ER) and progesterone receptor (PgR) content in patients with stage III and IV epithelial ovarian carcinoma

	ER positive (≥10 fmol) *n* (%)	ER negative (<10 fmol) *n* (%)	Total *n* (%)
PgR positive (≥10 fmol)	35 (19·6)	22 (12·3)	57 (31·9)
PgR negative (<10 fmol)	44 (24·6)	78 (43·5)	122 (68·1)
Total	79 (44·2)	100 (55·8)	179 (100)

$\chi^2 = 10{\cdot}11$, $P<0{\cdot}001$

dependences of the PgR effect on the other variables considered. As shown in Fig. 1, this exploratory analysis found that the effect of PgR on survival was much greater ($P = 0{\cdot}004$) for small residual tumours (≤2 cm) than for bigger ones (>2 cm). No other interactions with PgR were found. It follows that the PgR content can separate a group of seemingly (from the prognostic point of view) homogeneous group of patients with postoperative residual tumours ≤2 cm into a high-risk (PgR negative) group (with a 2-year survival probability of 51%) and a low-risk

Table 2. Correlation between oestrogen receptor (ER) and progesterone receptor (PgR) content and clinical pathological variables

		ER content				PgR content			
Variable	*n*	Negative (<10 fmol)	Positive (≥10 fmol)	χ^2	*P*	Negative (<10 fmol)	Positive (≥10 fmol)	χ^2	*P*
FIGO stage									
III	133	74	59	0·01	0·91	88	45	0·94	0·33
IV	46	26	20			34	12		
Histological type									
Serous	107	56	51	1·34	0·26	73	34	0·01	0·98
Others	72	44	28			49	23		
Histological grade									
Well	24	13	13	1·22	0·54	16	8	0·05	0·97
Moderate	52	26	26			36	16		
Poor	103	61	42			70	33		
Age (years)									
≤49	37	17	20	1·86	0·17	20	17	4·27	0·04
>49	142	83	59			102	40		
Ascites									
No	40	24	16	0·12	0·73	28	12	0·14	0·71
Yes	139	76	63			94	45		
Residual tumour (cm)									
≤2	78	42	36	0·23	0·63	51	27	0·49	0·48
>2	101	58	43			71	30		
Postoperative chemotherapy									
With cisplatinum	152	83	69	1·12	0·57	104	48	0·16	0·92
Without cisplatinum	22	14	8			15	7		
None	5	2	3			3	2		
Response to chemotherapy*									
Responder	109	61	48	0·58	0·44	66	43	5·61	0·01
Non responder	53	33	20			42	11		

* 17 patients could not be assessed due to early death ($n = 5$), only one cycle of chemotherapy ($n = 6$) and last to follow-up ($n = 6$).

Table 3. Univariate and multivariate analysis of prognostic variables for survival in patients with advanced epithelial ovarian carcinoma

		Univariate analysis		Proportional hazards regression			
Prognostic variables	*n*	Median survival (months)	Mantel-test *P*-value	RR	95% CI	Cox model *P*-value	Interaction* *P*-value
FIGO-stage							
III	133	20·7	<0·001	1·27	0·80–1·99	0·31	0·72
IV	46	8·6					
Histological type							
Serous	107	18·4	0·07	0·93	0·63–1·38	0·72	0·13
Others	72	12·6					
Histological grade							
Well or moderate	76	31·8	<0·001	2·16	1·43–3·25	<0·001	0·32
Poor	103	13·3					
Age (years)							
≤49	37	46·9	0·002	1·94	1·09–3·41	0·01	0·10
>49	142	14·8					
Ascites							
No	40	31·8	0·002	1·45	0·80–2·60	0·2	0·76
Yes	139	14·4					
Residual tumour (cm)							
≤2	78	32·1	<0·001	1·90	1·18–3.03	0·006	0·004
>2	101	12·5					
ER (fmol)							
<10	100	14·9	0·07	0·82	0·55–1·22	0·35	0·16
≥10	79	24·2					
PgR (fmol)							
<10	122	14·8	0·004	0·54	0·34–0·87	0·01	—
≥10	57	32·1					

*Test for interaction of PgR with individual prognostic variables within the Cox model framework. RR = relative risk, CI = confidence interval.

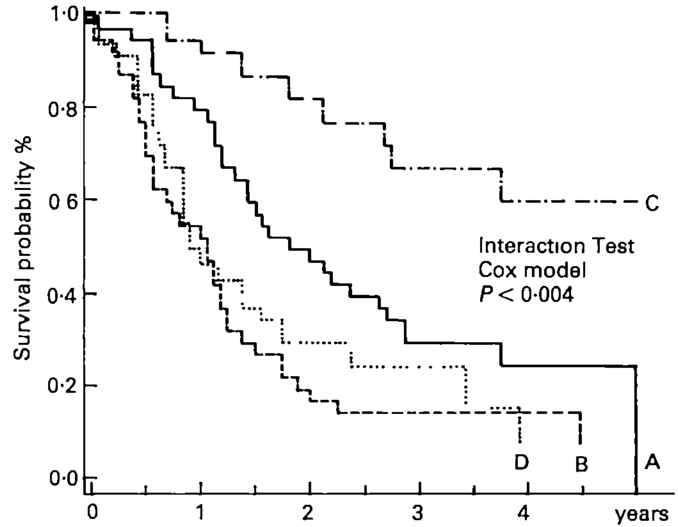
group (with a 2-year survival probability of 83%).

Discussion

Compared with most previous studies on the relevance of hormone receptor content in ovarian cancer, our series of patients is unusually homogeneous since we only included patients with epithelial ovarian cancer stage III and IV. Unlike others (Kauppila *et al.* 1983; Schwartz *et al.* 1985) we found no correlation between hormone receptor status and the differentiation of the tumour or any other patho-histological features. There only seems to be a correlation between the PgR content and the age of the patients. In younger patients PgR synthesis is possibly induced by endogenous oestrogen production shown by *in vitro* studies by Hamilton *et al.* (1984).

Furthermore, it is notable that 43 of the 54 PgR positive patients (80%) reacted positively to cytostatic chemotherapy compared with only 66 of the 108 PgR negative patients (61%), this difference is statistically significant (P=0·01).

This also seems to be contradictory to the results obtained by Teufel *et al.* (1983) and Bizzi *et al.* (1988). This connection between PgR content of the tumour cell and the response to chemotherapy is one of the possible explanations for the influence that PgR has on the survival prognosis for patients suffering from advanced epithelial ovarian cancer. An association between PgR content and proliferative activity of tumour cells, as found in endometrial carcinoma by Geisinger *et al.* (1986), could also offer an explanation for the prognostic relevance of PgR content. Results of this study could show a significant correlation between a high proliferative index of the tumour and a negative PgR content and a significant correlation between low S-phase activity and positive PgR content.



Patients at risk					
(A)RT≤2 PgR<10fmol	51	39	20	7	3
(B)RT>2 PgR<10fmol	71	30	8	5	2
(C)RT≤2 PgR≥10fmol	27	23	18	12	7
(D)RT>2 PgR≥10fmol	30	11	5	4	1

Fig. 1. Survival functions in patients with advanced epithelial ovarian carcinoma according to residual tumor (RT) mass and progesterone receptor (PgR) content

Therefore PgR-content seems to be associated with a low growth rate of the tumour.

Our results indicate that in epithelial ovarian cancer the PgR content of the tumour cell should be regarded as having independent prognostic relevance, as is the case in endometrial and breast carcinoma. The fact that the PgR content does not correlate with any of the traditional ovarian cancer prognostic factors makes it all the more valuable as an additional factor. Using the PgR status we could identify a high-risk group of patients (PgR <10 fmol/mg) within a group of patients normally categorized as low risk (residual tumours ≤2 cm) but who had a 2-year survival rate of only 51% in spite of chemotherapy containing cisplatin.

In conclusion we can say that the prognosis for patients suffering from epithelial ovarian cancer is related to PgR-status. Further studies should be conducted to examine the biological implications and the connections between PgR content of a tumour cell and the effect it has on cell proliferation, always bearing in mind the possibility of discovering new and improved methods of therapy.

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Gestrinone in the treatment of menorrhagia

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Summary. The role of gestrinone, 2·5 mg twice weekly, in treating proven menorrhagia (>80 ml) was examined in 19 women. They were treated for five cycles (2 placebo, 3 active), taking one capsule twice weekly. Placebo had no effect on menstrual blood loss (MBL). On gestrinone 10 women became amenorrhoeic, in five MBL was markedly reduced (5–74 ml) and four did not respond. In three of the non-responders submucous leiomyomas were found at subsequent hysterectomy. Follow-up periods showed a persistent reduction in MBL for nine women in the first post-treatment menstruation.

Menorrhagia is a significant clinical problem for which the consultation rate to general practitioners is 30·7 per 1000 (Morbidity Statistics in General Practice 1981–2). Gestrinone (13β - ethyl - 17α-ethinyl - 17 - hydroxygona-4, 9,11-trien-3-one; Roussel-UCLAF, Paris) is a 19-nortestosterone derivative that is an antiprogesterone and anti-oestrogen with some androgenic activity. It interacts with hypothalamic and pituitary steroid receptors to decrease the secretion of follicle stimulating and luteinizing hormones (Azadian-Boulanger *et al.* 1976, Kaupilla *et al.* 1985, Proulx *et al.* 1984) Gestrinone has been reported either to reduce menstrual blood loss or cause amenorrhoea when used to treat endometriosis at a dose of 2·5 mg twice weekly (Thomas & Cooke 1987*a* and 1987*b*) However, these reports were not substantiated by objective measurement of menstrual blood loss. It is an essential estimation since only 38% of women with self proclaimed menorrhagia have blood losses >80 ml per menstruation (Fraser *et al.* 1984, Hallberg *et al.* 1966). The present study was therefore undertaken to examine whether gestrinone reduced menstrual blood loss in women with proven menorrhagia (>80 ml per period) (Hallberg *et al.* 1966).

Patients and methods

The study included 37 women aged between 34 and 46 years complaining of regular heavy periods without intermenstrual bleeding who were recruited from the John Radcliffe Hospital gynaecology clinics. In all patients, pelvic examination and endometrial biopsy revealed no abnormality, and their plasma progesterone levels in the third week of the menstrual cycle were compatible with ovulation. Menstrual blood loss (MBL) was measured for two menstruations using the alkaline haematin technique, starting on the fourth period after endometrial biopsy to avoid any transitory effect of biopsy on MBL (Hallberg and Nilsson 1964). None of the women had received hormonal therapy for 4 months, nor inhibitors of prostaglandin synthesis nor antifibrinolytic agents for 1 month before MBL measurement In 20 women MBL was 80 ml, and 19 of them agreed to take part in the study. Patients gave written informed consent and the study was approved by the local ethics committee.

Methods

The study was a single-blind placebo-controlled trial of gestrinone 2·5 mg twice weekly. The patients received placebo for two menstrual

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cycles followed by 12 weeks of active medication. MBL was measured during placebo and active treatment and for a further 3 months follow-up after ceasing active treatment. Both placebo and active medication were started on day 1 of the first menstruation of each treatment and then taken regularly without a break. The reason for the design was that previous work suggested that the effect of gestrinone on MBL persisted after cessation of active treatment (Thomas & Cooke 1987*a* & *b*). The patients recorded bleeding patterns in daily diaries, and were reviewed monthly for side effects.

Menstrual blood loss is not normally distributed and therefore nonparametric analysis of variance was employed, and medians and ranges are quoted. However, for a given patient the mean was used because within-patient variability was not so marked. Thus for each patient an average mean MBL was calculated for the individual phases of the study (control, placebo, active treatment, and follow-up).

Results

Gestrinone was well tolerated and no patient withdrew from the study. Gestrinone administered for 12 weeks significantly reduced menstrual blood loss in 15 of the 19 patients in the study compared with the control cycles ($P<0{\cdot}01$) (Fig. 1). Placebo had no effect on MBL, duration of menstruation and cycle length.

All the patients studied had objectively proven menorrhagia with a median MBL of 173 ml (range 81–831 ml) in the two control cycles. The blood loss of the first menstruation when gestrinone was given, starting on day 1 of bleeding, was markedly increased compared with pretreatment cycles (median 213 ml, range 46–1421 ml). But further treatment caused amenorrhoea in five and then in 10 women after 4 and 12 weeks respectively. In the remaining nine women MBL was markedly reduced in five (5–74 ml), and four did not respond (91–476 ml). In the women who did not develop amenorrhoea, five reported more than three bleeds, with two having four and three having five bleeds respectively. The duration of menstruation was not significantly affected by gestrinone.

Spotting was reported by all the patients during the 12 weeks of active medication with a median of 11 days (range 1–23).

After stopping gestrinone, menstruation returned after a median of 25 days (range 2–40). In the first menstruation, MBL was still less than 80 ml (3–74 ml) in nine women. In the third menstruation MBL did not differ significantly from pretreatment values.

The most frequently reported side effects on active treatment were headaches, dizziness or giddiness and tiredness, reported by one third of the patients. However, their prevalence was greater in the pretreatment and placebo phases than during active treatment. Average weight gain during treatment was 2 kg which had been lost by 3 months after ceasing gestrinone. None of the patients became hirsute or developed voice changes during active treatment.

Nine patients have now undergone hysterectomy: five who had responded to gestrinone and the four who had not. In the patients who responded no pathology was found at surgery. In three of the four nonresponders, unsuspected submucous leiomyomas were found.

Discussion

Gestrinone is an effective treatment for menorrhagia causing amenorrhoea or reducing MBL in 15 of the 19 women studied. It is significant that previously undetected submucous leiomyomas were found in three of the nonresponders after hysterectomy. By their production of prostacyclin these lesions could account for the lack of response to gestrinone (Rees & Turnbull 1985). However, it would be expected that leiomyomas should shrink with gestrinone, but longer treatment may be required (Coutinho & Gonçalves 1989). Submucous leiomyomas can be detected at hysteroscopy and our data reinforce the view that this investigation should be carried out in menorrhagic women who do not respond to medical treatments.

A marked increase in blood loss was seen during the first period on gestrinone. The reason for this is unclear since in most cases only two or at the most three capsules would have been taken during this time. However, the increase did not deter the women from continuing the study. Also in half the women the first period after stopping treatment was significantly reduced. We concur with previous studies that placebo did not reduce MBL (Chimbira *et al.* 1980).

Our study again emphasises the importance of objective MBL measurements since only 20 of the 37 women (54%) referred with self proclaimed menorrhagia had blood losses exceeding 80 ml, with one woman losing only 14 ml (Hallberg *et al.*

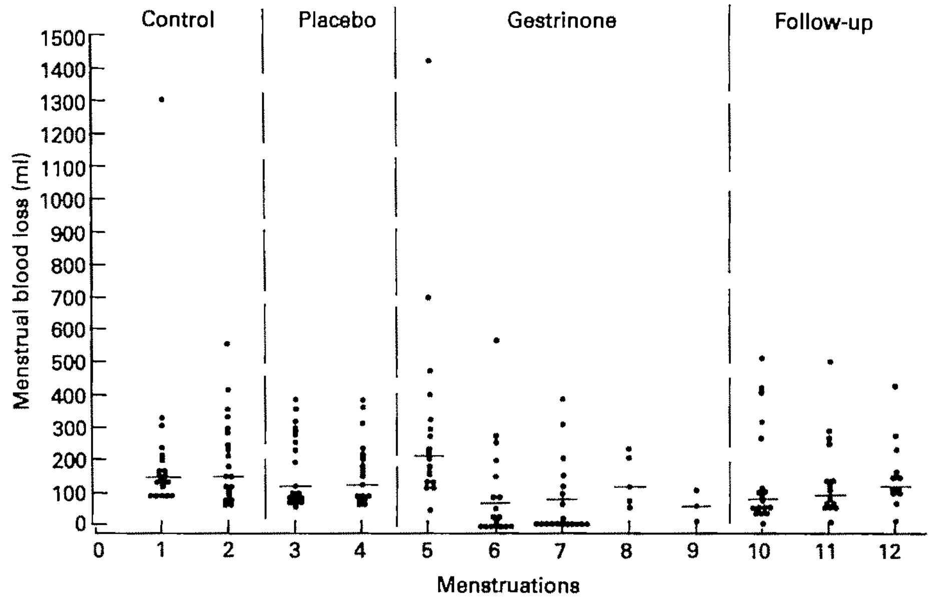

Fig. 1. Menstrual blood loss in a placebo controlled trial of gestrinone 2·5 mg twice weekly. Horizontal lines show the median values.

1966). Our percentage of women with objective menorrhagia is higher than the 38% found by Fraser *et al.* (1984), but it is probably accounted for by differences in patient selection.

The tolerance to gestrinone was good and there were no drop-outs throughout the whole study which lasted 10 months. We concur with Thomas and Cooke (1987*a*) that androgenic side effects were not found during gestrinone treatment.

In summary gestrinone has a beneficial effect on menorrhagia and should provide an alternative for women who are prepared to accept amenorrhoea during treatment.

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Uterine and fetal umbilical artery flow velocity waveforms in normal first trimester pregnancies

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Summary. In 85 normal singleton pregnancies between 8 and 13 weeks gestation, Doppler flow velocity waveform recordings were attempted from the left and right uterine artery and fetal umbilical artery. Acceptable waveforms were obtained from the uterine arteries in 83 and from the fetal umbilical artery in 61 of the 85 pregnancies. There was virtually no difference between the left and right uterine artery on average. The marked decrease in pulsatility (PI) and resistance (RI) indices from both uterine arteries reflects the ongoing process of secondary trophoblast invasion into the muscular part of the spiral arteries. Absent end-diastolic velocities were observed in 59 of 61 fetal umbilical artery flow velocity waveform recordings. PI values from the fetal umbilical artery suggest unaltered umbilical placental vascular resistance during the first trimester of pregnancy.

There have been many studies on uteroplacental and fetal umbilical artery blood flow velocity waveforms (FVW) as an indicator of placental perfusion during the second half of pregnancy (Campbell *et al.* 1983; Trudinger *et al.* 1985*a* & *b*; Cohen-Overbeek *et al.* 1985; Schulman, 1987; Reuwer *et al.* 1987). Particular emphasis has been placed on the decrease in down-stream impedence in uteroplacental vessels between 14 and 20 weeks gestation and this has been attributed to the secondary wave of trophoblast invasion in the myometrial portion of the spiral artery (Cohen-Overbeek *et al.* 1985). Recently, a few reports on uterine blood flow during the first trimester of pregnancy have appeared (Stabile *et al.* 1988; Deutinger *et al.* 1988).

The aim of the present study was to assess the pulsatility of uterine and fetal umbilical artery FVW recordings during normal first trimester pregnancies.

Subjects and methods

Maximum FVW from the uteroplacental and fetal umbilical circulation were collected by means of continuous wave Doppler (Doptek) without a two-dimensional imaging system. The carrier frequency of the Doppler transducer was 4 MHz, the cut-off level of the high-pass filter to eliminate low-motion artefacts was 150 Hz, the spatial peak temporal average intensity was less than 100 mW/cm^2. For recording Doppler signals from the uteroplacental circulation, the Doppler probe was orientated along the transverse axis of the uterus and the Doppler beam aimed at the lateral wall of the uterus. The FVW of the external iliac artery shows a pattern of high resistance with reverse flow in late systole and early diastole. The FVW of the internal iliac

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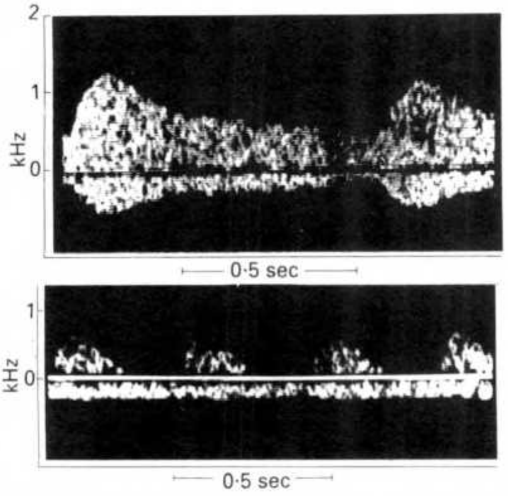

Fig. 1. Flow velocity waveforms from the uterine artery (Fig. 1a, top) and fetal umbilical artery (Fig. 1b, bottom) at 11 weeks gestation.

artery shows continuous forward flow during diastole, although it has a deep notch in relation to the closure of the aortic valve. With the Doppler transducer directed slightly more medially, Doppler signals in the opposite direction to those from the iliac arteries and originating from the uterine artery may then be obtained (Fig. 1). FVW recordings were made on both sides of the uterus. Recordings were only accepted as originating from the fetal umbilical circulation if signals from both the umbilical artery and vein were represented on the sonogram (on opposite channels) (Fig. 1). All measurements were made with the pregnant women in the semi-recumbent position.

The degree of pulsatility of the uterine and fetal umbilical arteries was quantified by calculating the pulsatility index (PI) and resistance index (RI). The PI is defined as the difference between peak systolic and end-diastolic velocity divided by the averaged flow velocity (Gosling and King, 1975). The RI was derived by dividing the result of the peak systolic flow velocity minus the end-diastolic velocity by the peak systolic velocity (Planiol and Pourcelot, 1975). The PI and RI were calculated over three consecutive cardiac cycles and averaged.

From November 1988 until April 1989, we investigated 85 singleton pregnancies between 8 and 13 weeks gestation referred from the antenatal diagnosis clinic. The women were either primiparous or had an uncomplicated obstetric history. Informed, oral consent was obtained in each instance. All subjects had gestation assessed by crown-rump length measurements and had had an uncomplicated pregnancy. For each gestational age the mean and SD of the PI and RI values were calculated. PI and RI were investigated for their relation with gestational age by linear regression.

In seven women the right and left uterine artery were scanned alternatively ten times in order to assess reproducibility.

Results

The with-in observer co-efficient of variation was 5·6%. Acceptable FVW recordings from the uterine arteries were obtained in 83 of the 85 pregnancies. PI calculations were made in all 83 pregnancies, whereas RI was calculated in 77 pregnancies. Mean PI and mean RI showed a statistically significant reduction with advancing gestational age in the left and right uterine artery separately and the average of both the left and the right uterine artery together (Table 1). The correlation coefficients of PI and RI with gestational age were −0·53 ($P<0{\cdot}001$) and −0·47 ($P<0{\cdot}001$), respectively.

Table 2 shows that there were differences

Table 1. Mean pulsatility and resistance indices from the left and right uterine artery separately and together in normal pregnancy between 8 and 13 weeks gestation

Gestation (weeks)		Pulsatility index				Resistance index		
	n	L	R	(L+R)/2	*n*	L	R	(L+R)/2
8	14	1·80 (0·70)	2·05 (0·93)	1·92 (0·69)	13	0·73 (0·15)	0·75 (0·17)	0·74 (0·12)
9	10	1·83 (0·65)	1·89 (0·62)	1·86 (0·61)	9	0·73 (0·15)	0·74 (0·16)	0·74 (0·14)
10	10	1·41 (0·30)	1·40 (0·67)	1·41 (0·42)	8	0·62 (0·10)	0·60 (0·18)	0·61 (0·12)
11	11	1·20 (0·68)	1·25 (0·65)	1·22 (0·59)	11	0·60 (0·19)	0·62 (0·15)	0·60 (0·13)
12	26	1·15 (0·60)	1·17 (0·55)	1·16 (0·47)	24	0·57 (0·14)	0·55 (0·16)	0·56 (0·11)
13	12	1·17 (0·43)	0·89 (0·38)	1·02 (0·30)	12	0·62 (0·16)	0·52 (0·16)	0·57 (0·12)

Results are mean (SD) values. L = left uterine artery; R = right uterine artery.

Table 2. Frequency and magnitude of difference between left and right uterine arteries in pulsatility index (PI) and resistance index (RI) values in normal pregnancies between 8 and 13 weeks gestation

	Differences in PI					Differences in RI				
Gestation (weeks)	*n*	L>R	*n*	R>L	R=L (*n*)	*n*	L>R	*n*	R>L	R=L (*n*)
8	7	0·64 (0·37)	7	0·86 (0·67)	—	6	0·15 (0·12)	7	0·16 (0·16)	—
9	3	0·27 (0·24)	4	0·35 (0·23)	2	4	0·07 (0·05)	5	0·08 (0·08)	—
10	5	0·50 (0·39)	4	0·60 (0·32)	1	4	0·17 (0·11)	4	0·12 (0·03)	—
11	5	0·54 (0·31)	6	0·53 (0·33)	—	5	0·16 (0·08)	6	0·20 (0·10)	—
12	12	0·48 (0·59)	12	0·51 (0·30)	2	12	0·17 (0·12)	11	0·16 (0·11)	1
13	8	0·60 (0·24)	3	0·43 (0·40)	2	9	0·18 (0·12)	3	0·16 (0·11)	—

Results are mean (SD) values of the differences between left uterine artery (L) and right uterine artery (R). L>R: left predominance; R>L· right predominance; L = R: no predominance

between the left and right uterine artery values for both PI and RI for each week of gestation. However, apart from week 13, there appears to be no essential difference in frequency or magnitude between left (L>R) and right (R>L) predominance for both PI and RI values. Satisfactory umbilical artery FVW recordings were obtained in 61 of the 85 pregnancies (74%). End-diastolic flow velocities were absent in 59 of the 61 recordings. Therefore, only PI values could be calculated. There appeared to be no relation between the umbilical artery PI and gestational age (Fig. 2). The mean PI at between 8 and 13 weeks gestation was 2·7 (SD 0·3).

Discussion

Acceptable uterine artery FVW recordings were obtained in almost all pregnancies, there were only two of poor quality due to maternal obesity. Our PI data confirm earlier reports of a difference in blood flow velocity between left and right uterine arteries during the first trimester (Deutinger *et al.* 1988; Stabile *et al.* 1988). The most likely explanation for the difference in PI and RI between the left and right uterine artery is that changes in down-stream impedance in the uterine artery supplying the placenta precede those in the uterine artery on the non-placental side of the uterus. Since clear delineation of the placenta was often not feasible at this early stage of gestation, no reliable information is available on the relation between uterine PI or RI and placental location. It appears, however, from this and previous studies that FVW should be recorded from both uterine arteries during the first trimester. Since the occurrence and magnitude of left (L>R) and right (R>L) predom-

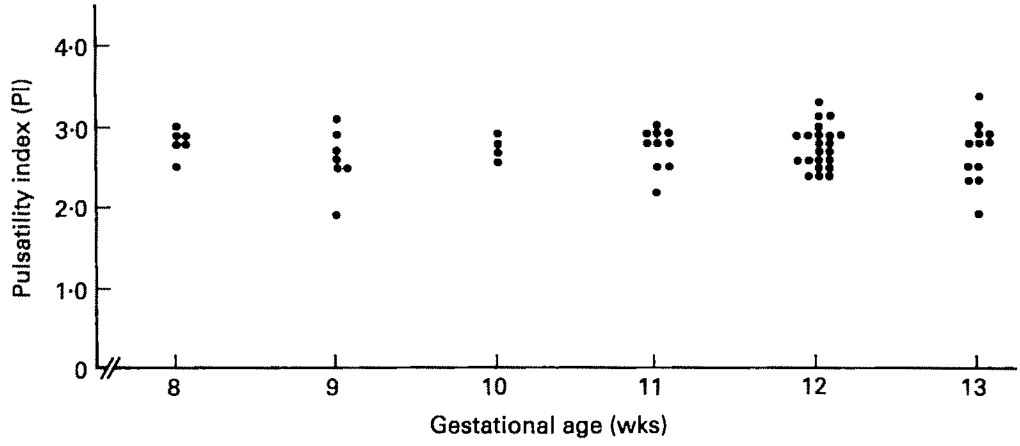

Fig. 2. Scattergram of PI values from the umbilical artery in 61 normal pregnancies between 8 and 13 weeks gestation.

inance in PI and RI values was not essentially different, for clinical purposes the mean PI and RI may be calculated from the combined values as an indicator of total down-stream impedence. During normal pregnancy, trophoblast invades the inner third of the myometrium as early as 8 weeks gestation and migrates through the entire length of the spiral arteries, the process being completed by approximately 20 weeks gestation (Pijnenborg *et al.* 1980). This process is probably responsible for the marked reduction in PI and RI for both uterine arteries with advancing gestational age in the present study. A similar pattern was described by Cohen-Overbeek *et al.* (1985) during the first half of the second trimester.

Fewer acceptable umbilical artery FVW recordings were obtained. The high failure rate of 26% was due mainly to our initial inexperience and, to a small extent, to maternal obesity. Approximately 80% of the failures occurred before 11 weeks gestation. In contrast to uterine blood flow, PI values from the umbilical artery showed no relation to gestational age, suggesting unchanged umbilical placental vascular resistance during the first trimester. Relating our present PI data to those obtained in late third trimester pregnancies (Wladimiroff *et al.* 1988) a reduction of 75% in mean PI from 2·7 to 0·7 apppears to occur during the last two trimesters of pregnancy.

It can be concluded that during the first trimester flow velocity indices should be calculated from both uterine arteries in order to establish downstream impedance at uterine level. The marked reduction in PI and RI in both uterine arteries during this period of gestation reflects the ongoing process of secondary trophoblast invasion into the muscular portion of the spiral arteries. The first trimester is characterized by unaltered umbilical placental vascular resistance.

Acknowledgment

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Apparent liver blood flow during pregnancy: a serial study using indocyanine green clearance

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Summary. Serial measurements of apparent liver blood flow and cardiac output were performed in 12 women at 12–14, 24–26 and 36–38 weeks of pregnancy and then at 10–12 weeks after delivery. Apparent liver blood flow was calculated from indocyanine green clearance. Cardiac output was measured by Doppler and cross-sectional echocardiography at the aortic valve. Postnatal apparent liver blood flow was 1·81 l/min and no significant change was demonstrated during pregnancy. In contrast cardiac output decreased from 7·46 l/min at 36–38 weeks gestation to 4·90 l/min after delivery. Apparent liver blood flow accounted for 24% of cardiac output during pregnancy. This increased to 37% after delivery.

During pregnancy cardiac output increases by 40–45% (Robson *et al.* 1989) and this is associated with substantial increases in renal, uterine and skin blood flow (Dunlop 1981; Metcalfe *et al.* 1955; Ginsburg & Duncan 1967). In contrast, the changes in liver blood flow during pregnancy have been poorly reported. Two cross-sectional studies using bromsulphthalein clearance have reported conflicting results (Munnell & Taylor 1947; Tindall 1975). The elimination of certain drugs is limited by liver blood flow and therefore changes during pregnancy have important pharmacokinetic and physiological implications.

Apparent liver blood flow can be measured by indocyanine green (ICG) clearance. Unlike bromsulphthalein, ICG does not exhibit extrahepatic removal and it has no enterohepatic circulation (Lorber *et al.* 1953; Cherrick *et al.* 1960; Leevy *et al.* 1967). Clearance following peripheral bolus injection has been validated against hepatic vein catheterization in animals and normal subjects (Grainger *et al.* 1983). The dye does not cross the placenta and it has been given to pregnant women without adverse effects in mother or fetus (Lees *et al.* 1967; Ueland *et al.* 1969; Probst *et al.* 1970; Mati *et al.* 1973; Mati and Kahuho 1974). Indocyanine clearance would therefore appear to be a safe and sensitive method of assessing liver blood flow during human pregnancy.

Cardiac output can be calculated from Doppler echocardiographic estimation of aortic velocity combined with cross-sectional echocardiographic measurement of aortic cross-sectional area. This method has been validated in pregnancy (Easterling *et al.* 1987) and allows reproducible measurements of cardiac output (Robson *et al.* 1987). We have used these techniques to study serially the changes in liver haemodynamics during normal pregnancy.

Subjects and methods

Fourteen healthy women were recruited from the antenatal clinic at between 8 and 12 weeks gestation. The first investigations were made at between 12 and 14 weeks gestation. Ultrasonic

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measurement of biparietal diameter confirmed menstrual dates in each subject. Investigations were repeated at between 24–26 weeks and 36–38 weeks of pregnancy and then 10–12 weeks after delivery. Two women failed to attend for one of these investigations and therefore serial data were available for analysis in 12 subjects, all of whom had an uneventful pregnancy and gave birth to a liveborn infant at term The details of this group are shown in Table 1.

The procedure was carefully explained to each woman and informed consent was obtained The experimental protocol was approved by the ethics committee of Durham Area Health Authority. The women were asked to attend having fasted and refrained from smoking for 4 h. Investigations were performed in a warm quiet room with the woman in the left semi-lateral position. After a 19-gauge cannula was inserted into an antecubital vein the woman rested for a minimum of 15 min.

Measurement of cardiac output

All the investigations were performed using a cross-sectional echocardiographic Doppler system (Diasonics). The principles and techniques used have been described previously (Robson *et al.* 1987). Ascending aortic blood velocities were recorded using an independent 2.0 MHz continuous wave transducer from the suprasternal notch. The system performed fast Fourier transform analysis of the Doppler signal and the output was converted to velocity of flow according to the Doppler equation:

$$V = \frac{f \times c}{2f_0 \times \cos\theta}$$

where V = velocity of erythrocytes, f = Doppler frequency shift, c = average speed of propagation of ultrasound in tissue, f_0 = emitting frequency of the transducer and θ = angle between the ultrasound beam and the direction of blood flow. The direction of the ultrasound beam was adjusted until the highest velocities with the least spectral dispersion were obtained. These velocities were stored in the system memory and it was assumed that they represented the velocities at the aortic orifice and that the ultrasound beam was parallel with flow. The area under the velocity curve (velocity integral) was determined by recalling the velocity output from the system memory and tracing from the baseline around the velocity curve using a tracker ball. The average of 8–10 consecutive beats was used for each determination. Heart rate was determined from the R–R interval of a simultaneously recorded electrocardiograph.

Aortic diameters were measured using a 5 MHz cross-sectional transducer. The aorta was imaged in the parasternal long axis plane and the orifice diameter was measured during systole (Robson *et al.* 1987). The diameters from five consecutive beats were averaged and the cross-sectional area calculated from $\pi \times (D/2)^2$ where D = mean aortic orifice diameter. Cardiac output (CO) was then calculated from the formula:

CO (ml/min) = heart rate (beats/min) × stroke volume (ml) where stroke volume = velocity integral (cm) × cross-sectional area (cm^2).

Table 1 Details of subjects studied

Number		12
Age (years)		25 (3)
Nulliparous		7
Gestation at delivery (days)		278 (8)
Birthweight (kg)		3 20 (0·47)
Mode of feeding·	Breast	6
	Bottle	6
Contraception·	Combined pill	4
	Progestogen-only pill	1
	Intrauterine device	2
	None	5

Values are mean (SD)

Measurement of apparent liver blood flow

The principles and techniques used have been described previously (Wynne *et al.* 1989). After collection of the initial blood sample, indocyanine green (ICG), 0·5 mg per kg, was injected intravenously over 20 s into a contralateral forearm vein. Heparinized blood (3–4 ml) was withdrawn at 1 min, 2 min and then every 2 min for 14 min and centrifuged at 3 000 **g** for 20 min, and the plasma removed. ICG concentrations were determined by absorption spectrophotometry (Pye Unicam PU8800) at a wavelength of 800 nm; Caesar *et al.* 1961). Plasma clearance of ICG (Cl_{ICG}) was calculated by dividing the dose by the area under the plasma concentration time curve (AUC) (determined by the trapezoidal rule):

$$Cl_{ICG} = \frac{\text{Dose}}{\text{AUC}}$$

and apparent liver blood flow was estimated as·

$$\text{Apparent liver blood flow} = \frac{Cl_{ICG}}{0{\cdot}74\,(1-\text{HCT})}$$

where HCT is the haematocrit, determined by

Coulter Counter (erythrocyte count × mean corpuscular volume) and 0·74 is the mean extraction ratio of ICG obtained by direct measurement in normal subjects (Wynne *et al.* 1989).

Statistical methods

A repeated measures analysis of variance was performed for each variable using the statistical package BMDP. Because of the problem of multiple significance testing, the differences between time points were compared using the studentized range at the 1% level:

$$\text{Range} = q_{(v)} \times (s \div \sqrt{n})$$

where $q_{(v)}$ is the critical value for comparing two time points, s^2 is the residual mean square with v degrees of freedom and n is the number of subjects. Any change greater than the studentized range was considered statistically significant.

Results

The weight, haematocrit, clearance and haemodynamic results are shown in Table 2. Haematocrit was reduced, relative to postnatal values, by 24–26 weeks gestation and thereafter showed no further change. No statistically significant difference was found in the peak 1-min plasma concentrations of ICG during the study. The mean postnatal values for ICG clearance and apparent liver blood flow were 897 ml/min and 1·81 l/min respectively. No significant changes were found in either of these measures during pregnancy. Heart rate, stroke volume and cardiac output were increased by the end of the first trimester and all showed a further increase between 12–14 and 24–26 weeks gestation. Cardiac output reached 7·51 l/min by 24–26 weeks gestation, representing an increase of 53% above postnatal values, and thereafter showed no further change. Apparent liver blood flow accounted for 37% of resting cardiac output after delivery. During pregnancy this percentage fell to between 24 and 27%.

Serum albumin concentration fell from a postnatal mean of 44·4 g/l to 40·9 g/l at 12–14 weeks of pregnancy. There was a further fall between 12–14 weeks and 36–38 weeks gestation (37·9 g/l). No significant changes were found in globulins, alanine aminotransferase, aspartate aminotransferase and γ-glutamyltransferase during pregnancy. Alkaline phosphatase was increased at 36–38 weeks of pregnancy (382 iu/l) relative to postnatal values (153 iu/l).

Discussion

This is the first study to report serial measurements of apparent liver blood flow (LBF) during pregnancy. The results suggest that, despite the marked increase in cardiac output, apparent LBF remains essentially unchanged throughout pregnancy. These findings confirm the results of Munnell & Taylor (1947) and Laakso *et al.* (1971) but are in disagreement with the 75% increase in LBF during pregnancy reported by Tindall (1975). Two of these studies calculated LBF from bromsulphthalein clearance; either from hepatic venous blood during peripheral infusion (Munnell & Taylor 1947) or from peripheral venous blood following peripheral bolus injection (Tindall 1975). However, a fraction of bromsulphthalein, varying from 5 to 7%, is excreted by extra-splanchnic mechanisms and the dye under-

Table 2 Weight, indocyanine green (ICG) clearance and haemodynamic results

	Gestation (weeks)			Postnatal (weeks)	SE	SR
	12–14	24–26	36–38	10–12		
Weight (kg)	63·4	68·2	71·8	63·5	0·6	2·3
Haematocrit (%)	35·4	33·7	33·3	37·4	0·6	2·3
ICG						
Peak concentration (μg/ml)	6·9	6·5	6·4	6·7	0·3	0·9
Clearance (ml/min)	815	929	893	897	60	237
Apparent liver blood flow (l/min)	1·71	1·92	1·80	1·81	0·13	0·50
Heart rate (beats/min)	77	84	84	67	2	7
Stroke volume (ml)	82	90	89	73	2	9
Cardiac output (l/min)	6·36	7·51	7·46	4·90	0·20	0·78
Apparent liver blood flow as % of cardiac output	27	26	24	37		

SE, standard error of the mean; SR, studentized range.

goes enterohepatic circulation (Lorber *et al.* 1953). Furthermore both the transfer and excretion of bromsulphthalen are altered during pregnancy (Tindall & Beazley 1965). Laakso *et al.* (1971) calculated 'minimal hepatic blood flow', measured in ml/kg, from the half life of ^{131}I-labelled human serum albumin. Blood volume, calculated using the same method, was reported to fall during pregnancy and the hepatic extraction of ^{131}I-labelled human serum albumin was erroneously assumed to be 100% (Shaldon *et al.* 1961). Thus measurements of LBF during pregnancy using these methods may be unreliable.

Indocyanine green (ICG) is a more suitable indicator for measuring LBF (Keiding 1987, Woodhouse & Wynne 1988). The dye is solely eliminated by the liver and has no enterohepatic circulation (Cherrick *et al.* 1960; Caesar *et al.* 1961; Leevy *et al.* 1967; Grainger *et al.* 1983). Measurements of LBF using ICG clearance have been validated in both animals and man (Grainger *et al.* 1983). The clearance of ICG is limited by LBF and by the capacity of the hepatic active transport mechanisms. The delivery of ICG to the liver is rate limiting at low doses such as those used during the present study (Paumgartner *et al.* 1970). During this study a number of assumptions have been made when using ICG clearance to calculate apparent LBF. Firstly, ICG was assumed to be distributed instantaneously into the plasma compartment where it was firmly bound to plasma proteins. Confirmatory evidence for this was provided by Cherrick *et al.* (1960). Changes in distribution volume during pregnancy would not affect the results because clearance is independent of distribution volume Secondly, it was assumed that the hepatic extraction ratio of ICG was 0·74 and that there was no change in this ratio during pregnancy. The value of 0·74 was derived from six previous studies in which direct measurements were performed in young normal non-pregnant adults (Wynne *et al.* 1989). Confirmation that changes in ICG clearance during pregnancy solely represent changes in LBF rather than impairment of uptake or transport of the dye into hepatocytes would require hepatic vein catheterization. Ethical constraints prevent such a study in man and, as far as the authors are aware, extraction ratios in pregnant animals have not been reported. Finally it was assumed that the elimination of ICG followed exponential or first-order (dose independent) kinetics. Exponential decay, at least during the first 10–20 min after administration, has been demonstrated by Cherrick *et al.* (1960) and our plasma concentration data together with those of Wynne *et al.* (1989) would confirm this. Although other workers have suggested that the kinetics may be more complex (Burczynski *et al.* 1987), calculation of clearance by the method described (dividing the dose by the area under the plasma concentration-time curve) has the advantage that it is independent of the kinetic model.

The afferent blood supply to the liver is from two sources, the hepatic artery and the portal vein. Resting LBF has generally been reported to be between 1·5 and 1·7 l/min in healthy resting adults (Bradley *et al.* 1952, Wilkins *et al.* 1952, Cherrick *et al.* 1960). However, Wynne *et al.* (1989) demonstrated that LBF declines with age and analysis of their data for women under 35 years of age yields a mean apparent LBF not significantly different from the mean non-pregnant value reported in the present study Interestingly, Tindall (1975) reported a mean non-pregnant LBF of the only 801 ml/min. This is considerably lower than all other reported figures and suggests that the method used systematically underestimated LBF, at least in the non-pregnant subjects.

The increases in cardiac output reported here confirm the findings of our previous study in which cardiac output was measured by Doppler echocardiography at three intracardiac sites during pregnancy (Robson *et al* 1989). The present results suggest that the liver receives little, if any, of this increased cardiac output and that LBF, expressed as a percentage of total cardiac output, falls during pregnancy. This is in agreement with previous animal studies (Peeters *et al.* 1980; Johnson *et al.* 1985). None of the previous studies of LBF in human pregnancy has included measurements of cardiac output

The results of the present study would suggest that apparent LBF does not change significantly during pregnancy, despite the large increase in cardiac output. Thus the elimination of drugs with a high hepatic extraction ratio is unlikely to change substantially during pregnancy.

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C-reactive protein and serum amyloid A protein in pregnancy and labour

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Summary. Serum levels of C-reactive protein (CRP) and amyloid A protein (SAA) were measured prospectively using immunoradiometric assays in normal pregnant women, newborn infants and women with prelabour rupture of membranes (PROM), focusing on the peripartum period. CRP levels in 50 healthy women at 38 weeks gestation did not differ significantly from previously established normal values. CRP levels in 67 healthy women sampled serially in labour from admission to 96 h postpartum confirm the physiological occurrence of a major acute phase response. The serial CRP levels of 16 women with PROM did not differ significantly from the wide range of CRP levels found in the normal postpartum period. This complicates the use of CRP as an early predictor of clinical chorio-amnionitis. Serial SAA levels in 17 women at 38 weeks gestation, immediately postpartum and 24 h postpartum showed a parallel rise to CRP in the peripartum period. Significant differences between maternal and neonatal CRP and SAA levels were demonstrated, implying a lack of transplacental transfer during labour.

C-reactive protein (CRP) and serum amyloid A protein (SAA) are the most sensitive acute phase proteins in man rising up to 1000-fold in infection, neoplasia or tissue necrosis (Pepys & Baltz 1983). A rising concentration of CRP during pregnancy as well as consistent, postpartum elevations have been established (Romem & Artal 1985). Explanations suggested for this acute phase response in apparently normal pregnancy have included placental ageing, rising oestrogen levels, cellular injury and a rise in prostaglandins during labour (Romem & Artal 1985).

Prelabour rupture of membranes (PROM) remains an extremely important cause of perinatal morbidity and mortality as a result of the accompanying increased risk of chorio-amnionitis (Perkins 1982). Several workers have suggested that elevated CRP is a reliable, early predictor of clinical chorio-amnionitis (Evans *et al.* 1980; Hawrylyshun *et al.* 1983; Romem & Artal 1984; Ismail *et al.* 1985; De Souza *et al.* 1987; Salzer *et al.* 1987) as well as a marker for failed tocolysis in preterm labour (Handwerker *et al.* 1984; Potkul *et al.* 1985; Dodds & Iams 1987). This is important as the erythrocyte sedi-

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mentation rate (ESR) is of little value in monitoring inflammatory states in pregnancy (Ostensen 1984). In contrast Farb *et al* (1983) found that elevated levels of CRP did not reliably predict clinical or histological chorioamnionitis or neonatal sepsis. Recently other workers (Fisk *et al.* 1987; Ernest *et al.* 1987) have also reported that CRP levels have limited value in managing patients with PROM. Cut-off points for the upper normal level of CRP in these studies were arbitrarily selected and ranged from 7–20 μg/ml although in 468 healthy adult volunteer blood donors Shine *et al.* (1981) found CRP levels of <3 μg/ml in 90% of subjects and a median value of 800 ng/ml.

As a prerequisite for analysing the acute phase response associated with pathology in pregnancy and labour, there is a need to establish normal values for CRP and SAA. Towards this end, Romem *et al.* (1985) measured CRP and Ostensen *et al.* (1985) SAA in pregnancy and in the postpartum period. Romem *et al.* (1985) observed the extent of the acute phase response at 12, 24, 36 and 48 h after normal spontaneous vaginal delivery as well as a gradual rise in CRP levels throughout pregnancy but neither study included serial values obtained during labour.

In view of this uncertainty concerning the normal values for CRP in normal pregnancy, labour and postpartum periods and the limited experience with SAA in pregnancy, we determined these acute phase protein levels using sensitive immunoradiometric assays in normal pregnant women, newborn infants and women with PROM focusing on the peripartum period.

Subjects and methods

Blood samples for CRP level determination were obtained with informed consent from the following four groups of women: (1) 50 healthy pregnant women with negative urine cultures at 38 weeks gestation; (2) 67 women in labour with intact membranes who were sampled on admission, 2 h later or when the cervix was 8 cm dilated, immediately after delivery and again 24, 48 and 96 h later; (3) nine women with PROM of <6 h duration who were sampled on admission, 2 h later or when the cervix was 8 cm dilated, immediately after delivery and 24 h later; (4) seven women with PROM of >48 h duration who were sampled on admission, 2 h later or when the cervix was 8 cm dilated, immediately after delivery and 24 h later.

In groups 2, 3 and 4, women not serially sampled at more than two of the stated times were excluded from the study. Cord blood samples were obtained concomitantly with the immediate postpartum maternal samples. A further six women were sampled every 3 h for 15 h after induction of labour was attempted by increasing amounts of intravaginal prostaglandin E_2 (PGE_2) tablets administered every 4 h.

Serial blood samples for SAA determinations were also obtained from 17 healthy pregnant women at 38 weeks gestation, immediately postpartum (with a concomitant neonatal cord blood specimen) and 24 h postpartum

Serum samples were stored at −20°C after separation from venous blood clotted at room temperature. Samples were thawed and run in batches to determine CRP and SAA concentrations. Concentrations of CRP were measured by a magnetisable cellulose solid phase immunoradiometric assay, standardized with pure isolated human CRP (De Beer & Pepys 1982). SAA levels were measured with a similar immunoradiometric assay standardized to acute phase high density lipoprotein-3 (HDL_3) (De Beer *et al.* 1982; Godenir *et al.* 1985). The sensitivity of the CRP assay was 10 ng/ml and of the SAA assay 100 ng/ml. Inter- and intra-assay coefficients of variation were <10%. The statistical significance of differences between groups was investigated by the Wilcoxon rank sum test, Kruskal Wallis test, Mann–Whitney *U*-test and the Freedman two way analysis of variance.

Results

The CRP concentrations in pregnancy, labour and postpartum in the three groups sampled serially are shown in Fig. 1. At 38 weeks gestation the median CRP concentration of 1·5 μg/ml (95% CI 0·1 to 2·9 μg/ml) did not differ significantly from the normal values established by Shine *et al.* (1981) A significantly increased CRP level at the time of admission was found in normal pregnancy with a median of 7·5 μg/ml (range 0·16–32 μg/ml) ($P<0·0001$). The CRP levels peaked at 24 h after delivery in normal pregnancy with significantly higher concentrations than the values immediately after delivery ($P<0·0001$), 48 h postpartum ($P<0·05$) and 96 h postpartum ($P<0·05$). The median value for CRP at 96 h after delivery in normal pregnancy was 15 μg/ml and the range extended to

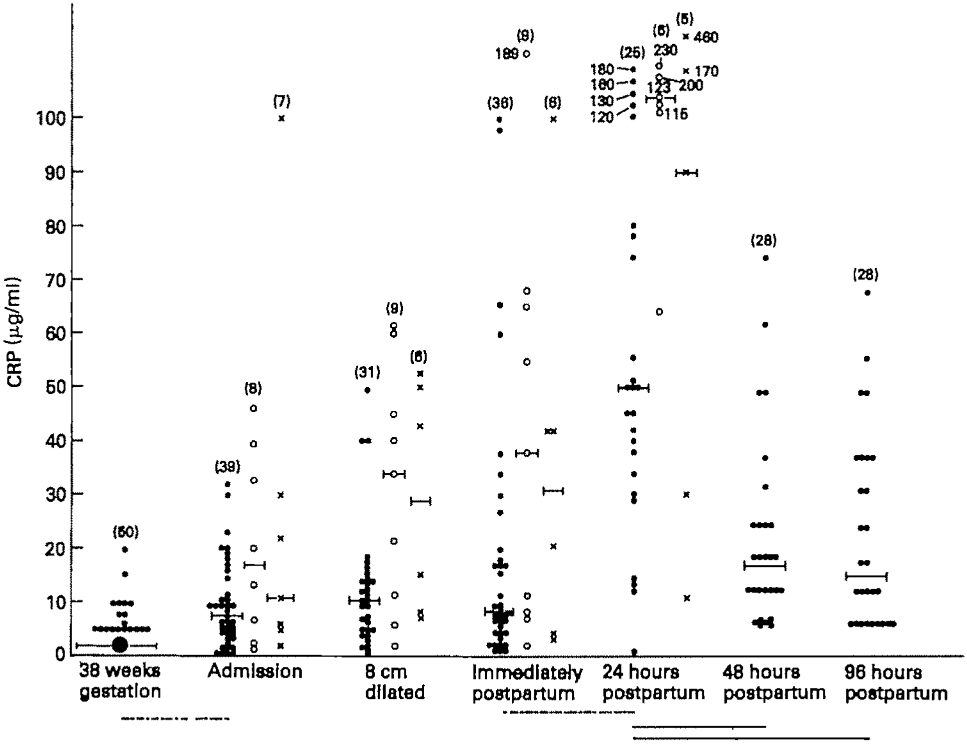

Fig. 1. Serial C-reactive protein (CRP) in pregnancy, during labour and postpartum in healthy women (●), women with <6 h duration of rupture of membranes (○) and women with >48 h duration of rupture of membranes (×). The distribution and the median of values are shown.—$P<0{\cdot}05$; ----- $P<0{\cdot}0001$

68 µg/ml. No statistically significant difference was found between women with normal pregnancy, women with PROM of <6 h and >48 h duration

In Fig. 2 serial SAA levels are shown in normal healthy women in pregnancy and labour. There is a statistically significant difference between values at 38 weeks gestation, immediately postpartum ($P<0{\cdot}05$) and 24 h postpartum ($P<0{\cdot}05$). Table 1 shows the comparative CRP and SAA levels in normal women, normal pregnant women at 38 weeks gestation and immediately after delivery, and in cord blood. Maternal and neonatal CRP ($P<0{\cdot}0001$) and SAA ($P<0{\cdot}05$) levels differ significantly.

CRP concentrations did not increase appreciably in those women in whom induction of labour was attempted with intravaginal PGE_2 tablets when sampled serially every 3 h for 15 h.

Discussion

The CRP concentrations obtained in pregnancy, during labour and postpartum extend the data of Romem *et al.* (1985) for normal pregnancy, providing more information on the changes in the peripartum period. Their finding of a tendency to an increased level of CRP during gestation is not confirmed by our data at 38 weeks gestation.

The significantly increased CRP level at the time of admission provides evidence for an established acute phase response well before any trauma of parturition, and points to preceding interleukin-I (IL-1) and interleukin-6 (IL-6) release by activated macrophages leading to increased hepatic synthesis of CRP and SAA as well as other acute phase proteins (Dinarello 1984). Given the fact that the half-life of CRP is 6–8 h (Pepys & Baltz 1983), it is possible that the onset of this acute phase response coincided with the initiation of labour.

The physiological acute phase response demonstrated in established labour could be linked to the proposed role of CRP as a non-specific circulatory scavenger of tissue and cellular constituents not normally found in plasma (Pepys & Baltz 1983). Clearance of chromatin by pentraxins (CRP and serum amyloid P-component) might be particularly important (Robey *et al.* 1984; Pepys & Butler 1987).

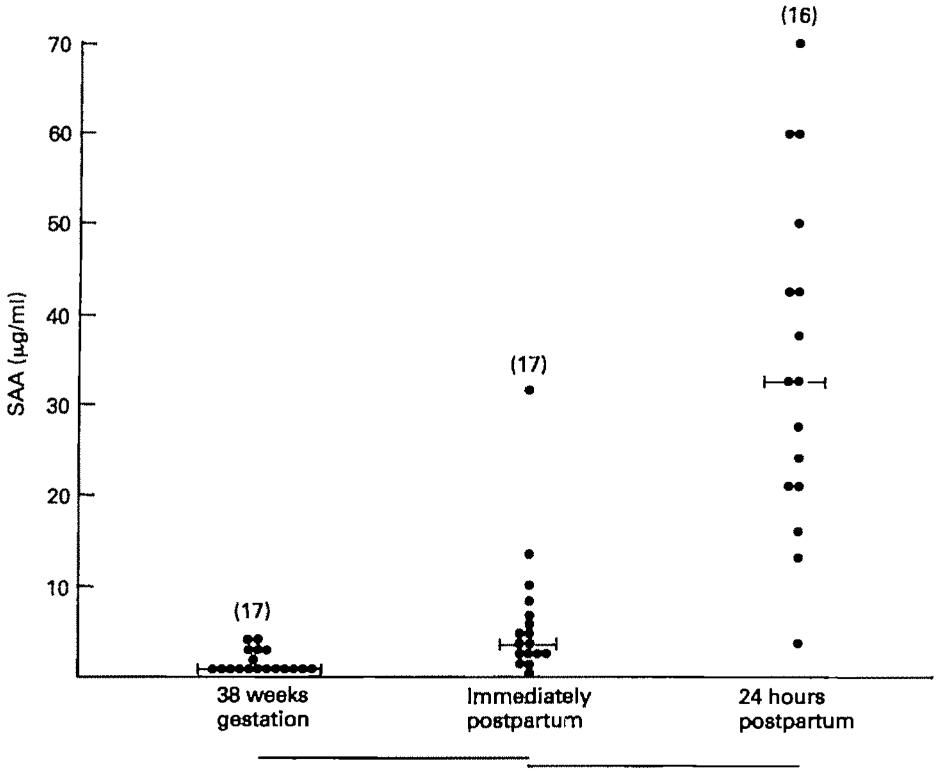

Fig. 2. Serial serum amyloid A protein (SAA) in healthy women in pregnancy, labour and postpartum. The distribution and the median of values are shown —$P<0 \cdot 05$.

Our findings confirm the peak in CRP levels at 24 h after delivery in normal pregnancy found by Romem *et al.* (1985). This contrasts with a study by De Beer *et al.* (1982) in which CRP peaked around 50 h after the onset of myocardial ischaemia and infarction. This provides additional circumstantial evidence that the induction of the physiological acute phase response of labour takes place at the time when labour is initiated.

It is evident that a significant acute phase response is still present 96 h postpartum in normal pregnancy. This wide range overlaps with those values found in women with PROM of <6 h and >48 h duration. This finding complicates the use of CRP as an early predictor of clinical chorio-amnionitis.

An acute phase response could not be elicited by the use of intravaginal PGE_2 tablets for the induction of labour. This is in contrast to Whicher *et al.* (1982) who found that infusion of PGE_1 in the man can cause increases in concentrations of CRP and other acute phase proteins, but in accordance with the demonstration by Strachan *et al.* (1984) that indomethacin in athletes had no effect on the acute phase response elicited by long distance running.

The serial SAA levels obtained extend the data of Ostensen *et al.* (1985) and establish that SAA parallels the rise in CRP during the peripartum period. The function of SAA is unknown, but it may be clinically useful in monitoring the acute phase response (Pepys & Baltz 1983). The significant differences between maternal and neonatal CRP and SAA imply a lack of transplacental transfer of these proteins during labour. Any increase in CRP or SAA in the newborn could therefore signify either increased neonatal production as a consequence of infection or trauma or a compromise in placental integrity with subsequent transfer.

In conclusion, the present study confirms the physiological presence of a major acute phase response in the normal peripartum period up to 96 h after delivery and establishes data for serial CRP levels during normal labour. The extremely wide range of CRP levels in the normal postpartum period up to 96 h demonstrates the difficulty of using CRP as a marker of

Table 1. C-reactive protein (CRP) and serum amyloid A protein (SAA) levels in pregnancy, labour and newborn

	Normal non-pregnant	At 38 weeks gestation	Immediately after delivery	Cord blood
CRP (μg/ml)				
Median	0·8*	1·5	8·5	0·6
Range	0·07–2·9	0·02–20	1·6–100	0·14 –24
n		50	36	38
SAA (μg/ml)				
Median	1·2†	0·45	3·5	0·04
Range	0·2 –2·5	0·02–2·9	0·2– 31	0·008–2·1
n		16	17	17

*Shine *et al* (1981)
†Ostensen *et al* (1985)

maternal infection in this period. Studies that focus on an interruption in the serial decline phase of CRP postpartum could be useful in maternal pathological processes.

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Unsatisfactory colposcopy and the response to orally administered oestrogen: a randomized double blind placebo controlled trial

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Summary. Thirty-six women with dyskaryotic cervical smears and unsatisfactory colposcopy were randomly allocated to receive either 30 μg ethinyl oestradiol or placebo daily by mouth for 10 days. Thirty-four women were available for review (17 women in each of the two groups), full colposcopic inspection of the transformation zone was possible in a significantly greater proportion of the oestrogen treated group (70% versus 23%, $P<0{\cdot}01$). As most diagnostic conizations are currently performed on the basis of unsatisfactory colposcopy, the use of oestrogen medication followed by colposcopic reassessment should permit a reduction in the number of patients subject to operation.

Of all patients referred for colposcopic assessment because of abnormal cervical cytology, around 10–20% will require diagnostic cone biopsy (Singer & Walker, 1982) usually because the cervical transformation zone (TZ) extends into the endocervical canal and a satisfactory colposcopic examination is not possible.

In view of the potential morbidity of the operation it is desirable to limit the use of diagnostic conization if possible, particularly as subsequent histological examination of the cone specimen often fails to reveal significant disease (Lopes *et al.* 1989). Treatment with relatively high doses of oestrogen has been reported to facilitate examination of the TZ in patients whose initial colposcopic assessment was unsatisfactory (Prendiville *et al.* 1986).

In a recent study of microcolpohysteroscopy before diagnostic conization, both the position of the new squamocolumnar junction and the frequency of negative cone biopsy appeared to be influenced by oral contraceptive use (Saunders *et al.* 1990). In view of this observation, the present study was designed to assess the effect of treatment with 30 μg of ethinyl oestradiol in patients with an unsatisfactory colposcopy at the time of initial assessment.

Subjects and methods

The study was conducted between November 1988 and June 1989 in the colposcopy clinic at the Northern General Hospital, Sheffield. Eligible patients were those with dyskaryotic smears in whom the upper limit of the TZ was not colposcopically visible due to its endocervical location.

Exclusion criteria included current use of oestrogen-containing preparations, previous illness contraindicating oestrogen use (i.e. liver disease, thromboembolic disease, hypertension,

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breast carcinoma) or evidence of invasive cervical carcinoma on cytological or colposcopic examination. After colposcopic examination had failed to demonstrate the upper limit of the TZ, patients were asked to participate in the study. The trial was double blind and placebo controlled. Randomization was performed by hospital pharmacy staff using random number allocation.

The oestrogen or placebo tablets were placed in individually numbered medicine containers and stored in the colposcopy clinic. Active treatment consisted of 30 μg of ethinyl oestradiol given daily by mouth for 10 days. Premenopausal patients were asked to start taking the medication on the fifth day of the menstrual cycle and return appointments were planned to coincide with the tenth day of treatment (i.e. around midcycle). Post menopausal patients started the treatment at any convenient time.

If the new squamocolumnar junction was fully visible at the repeat colposcopy, a biopsy was taken of any atypical areas within the TZ. Patients with persistent cytological abnormality and in whom the squamocolumnar junction was not visible were advised to have excisional conization. The interval between examination and surgery was at least 6 weeks to allow any effect of active treatment on the coagulation system to subside.

Statistical analysis

Assuming a 65% response in the active treatment group and a 10% response in the placebo group, approximately 17 patients in each group would be required to demonstrate a difference in outcome, statistically significant at the 5% level and with a power of 90%.

Results

Of 36 patients entered into the study, one did not take the medication as she was found to be pregnant and in one other patient the follow-up visit was mistimed and colposcopy could not be performed because of uterine bleeding.

Table 1. Characteristics of the patients in the two study groups

Characteristic	Oestrogen (n=17)	Placebo (n=17)
Age (years)		
Mean	40	38
Range	(21–62)	(23–56)
Parity		
Mean	1·8	2·1
Range	(0–7)	(0–4)
Postmenopausal (n)	4	3

Analysis of the outcome in the remaining 34 patients revealed that 17 had received oestrogen and 17 placebo. The two groups were well matched for age, parity and menopausal status (Table 1).

On colposcopic review the TZ was fully visible in a significantly greater proportion of patients in the oestrogen group than in the placebo group ($P<0{\cdot}01$, χ^2-test) and as a result fewer patients required diagnostic conization (Table 2).

No clinically significant side effects were reported by any of the patients in the study, particularly in respect of nausea and vomiting.

Discussion

It is recognized that both pregnancy and oral contraceptive use are associated with cervical eversion, whereby columnar epithelium becomes visible on the ectocervix (Coppleson & Reid, 1966; Carbia *et al.* 1968).

The histological changes seen in these two situations are similar, namely an increase in the vascularity of the cervix, an increase in the number and size of glands, with active secretion of mucus and stromal oedema.

Maqueo *et al.* (1966) suggested that the intensity of these changes was related to the level and duration of exposure to progestational agents, although Mingeot & Fievez (1974) concluded that it was not possible on the available evidence to determine whether the oestrogenic or progestogenic component or both were responsible for the observed cervical changes. What is beyond question, however, is that all of these changes will tend to promote an increase in cervical vol-

Table 2. The effect of treatment with oestrogen on the visibility of the transformation zone and on the need for diagnostic conization

	Oestrogen (n=17)	Placebo (n=17)	Odds ratio (95% CI)
TZ fully visible	12	4	7·8 (1·6 to 36)
Diagnostic conization	4	10	4·6 (0·06 to 20)

CI = confidence interval.

ume which, because of the fixation of the lateral cervix may result in an eversion of endocervical mucosa, (a view first proposed by the Bonn-Cologne Group (Hamperl & Kaufmann, 1959)) Certainly in pregnancy, the size of the cervix and the degree of eversion are correlated (Coppleson & Reid, 1966). The frequency with which eversion occurs in pregnancy may also account for the fact that unsatisfactory colposcopy is rare at this time (Stafl & Mattingly, 1973).

Our results suggest that cervical eversion may occur in response to relatively small amounts of orally administered oestrogen alone. This in turn allows improved inspection of the TZ with the result that some patients with a previously unsatisfactory colposcopic examination may be spared diagnostic conization. It is also possible that oestrogen improves colposcopic examination by promoting favourable changes in cervical consistency and cervical mucus.

This approach to the problem of unsatisfactory colposcopy was first suggested by Paterson *et al.* (1982) when it was noted that in three of six postmenopausal patients the TZ became fully visible after three months treatment with sequential mestranol and norethisterone.

Prendiville *et al.* (1986) reported that oestrogen alone in the form of 100 μg daily for five days allowed complete visibility of the TZ in 16 of 25 patients with previously unsatisfactory colposcopy. This was, however, an uncontrolled study which is perhaps unsatisfactory given the subjectivity of the endpoint under scrutiny. In addition 100 μg of ethinyl oestradiol will produce nausea in a large proportion of patients and there must be concern as to the potentially serious effects of such a dosage on the coagulation system.

It appears from the results of the present work that a significantly smaller dosage of oestrogen may be equally effective in producing the desired changes in the cervix.

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Assessment of menstrual blood loss using a pictorial chart

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Summary. Objective menstrual blood loss measurements (in ml) were compared with the score obtained from a pictorial blood loss assessment chart (PBAC) which took into account the degree to which each item of sanitary protection was soiled with blood as well as the total number of pads or tampons used. Twenty eight women used the chart during 55 menstrual cycles and a single observer assessed 122 cycle collections in a similar manner. A pictorial chart score of 100 or more, when used as a diagnostic test for menorrhagia, was found to have a specificity and sensitivity of >80%. Demonstration of the relation between self assessed pictorial chart scores and the objective measurement of blood loss enables us to provide a simple, cheap and reasonably accurate method of assessing blood loss before embarking upon treatment.

Menorrhagia is a common complaint of women presenting to general practitioners and gynaecologists. Information obtained from the history alone is an unreliable indicator of true menorrhagia (Barer & Fowler 1936; Haynes *et al.* 1977; Rees *et al.* 1982). Menorrhagia is defined subjectively as excessive or prolonged loss of blood on a regular cyclical basis or objectively as menstrual blood loss of ≥80 ml for the whole period (Hallberg & Nilsson 1966). The objective assessment of menstrual blood loss uses a specialized and time-consuming technique which is not available for routine clinical use. It is, however, an extremely valuable tool in scientific research.

Simple non-laboratory methods such as tampon and pad counting and the weighing of such blood-stained material have proven to be of little value (Chimbira *et al.* 1980; Rankin *et al.* 1962). In an attempt to create a more accurate yet simple method of assessment, a pictorial blood loss assessment chart (PBAC) was devised which, in addition to recording the number of towels and tampons used, took into account the degree to which individual items were soiled with blood. This factor is essential, as women use a widely varying quantity of towels and tampons to collect similar amounts of menstrual blood (Fraser *et al.* 1984).

Subjects and methods

The women included in this study were participating in a clinical trial which involved the accurate objective assessment of menstrual blood loss (the results of this comparative drug trial are to be published separately). These participants were provided with sanitary protection (Tampax and Kotex Fems super plus tampons and Kotex Simplicity size 2 towels) which, when they had been used, were collected in plastic bags and returned to the department. Thirty of these participants who consecutively attended the department were also given a pictorial blood loss

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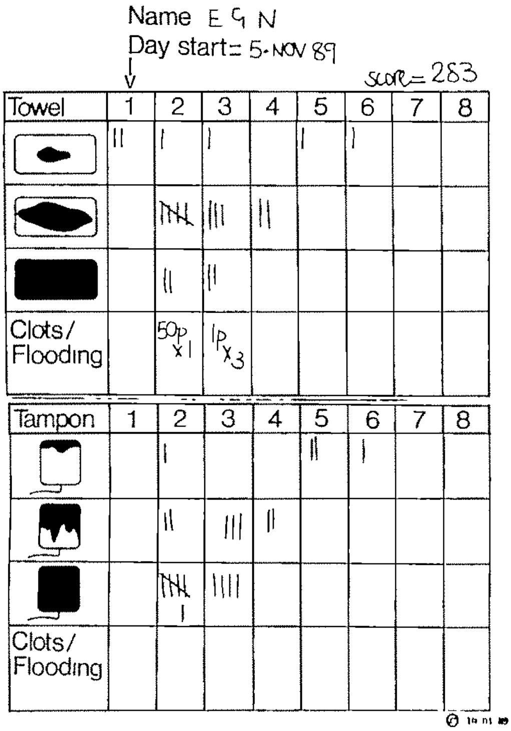

Fig. 1. Assessment of menstrual blood loss using the pictorial blood loss assessment chart (PBAC)

assessment chart (PBAC) (Figure 1) for completion with their next menses, an explanation of how it should be used and a simple instruction leaflet. The chart consisted of a series of diagrams representing lightly, moderately and heavily soiled tampons or towels, a mark being made in the appropriate box at the time that each item of sanitary protection was discarded and if sufficient were used, these were counted in groups of five. In addition, passage of clots (size equated with that of coinage) and episodes of flooding were recorded.

After the menses, the pictorial chart was returned, together with all the soiled sanitary material. The towels and tampons were then subjected to a similar assessment by a single gynaecologist (JMH) who completed a pictorial blood loss assessment chart using the same criteria as the patient, having not seen the patient's own pictorial chart assessment. Finally, the blood content of the sanitary material was quantified using the alkaline haematin method for determination of menstrual loss (Hallberg and Nilsson 1964) This is reliable and is considered the standard technique for estimating the blood content in millilitres. An additional 67 menstrual collections were assessed only by the gynaecologist using the pictorial chart and the alkaline haematin method, before and after the charts were distributed to the women in the study. This enabled the pictorial method to be investigated in a larger group of women.

A scoring system was devised. Known volumes of expired venous blood were applied to the same types of towels and tampons as were used by the women in order to produce the appearances depicted on the chart. These items could absorb different volumes of blood and yet remain visually similar. Consequently, the scores were proportional, but not necessarily equivalent, to the blood volume in ml. The scores assigned were 1 for each lightly stained tampon, 5 if moderately soiled and 10 if it was completely saturated with blood. The towels were given ascending scores of 1, 5 and 20. Small and large clots scored 1 and 5 respectively. The total numerical score for each pictorial chart made it possible to compare the assessment by the patient using the pictorial chart with the assessment by the gynaecologist using the pictorial chart and the actual blood loss measured with the alkaline haematin method.

Statistical analysis

The pictorial chart scores recorded by the gynaecologist and the patients were assessed by the technique of measurement of agreement as described by Bland & Altman (1986) as these data were expressed in comparable units. A Spearman Rank correlation coefficient was used for correlations between data.

Results

Thirty women were admitted to the study. Their mean age was 39 years (range 27–48). Two of these women were unable to complete the chart because they found it difficult to understand The remaining 28 women monitored between one and three cycles each, giving a total of 55 patient-assessed menstrual cycles. The patients' pictorial chart scores ranged from 5 to 456 (median 121). The gynaecologist's pictorial chart scores ranged from 6 to 360 (median 87). Blood loss measured with the alkaline haematin method ranged from 2 to 366 ml (median 74 ml).

The relation between measured menstrual blood loss and the pictorial chart score recorded by the woman is shown in Figure 2. The relation

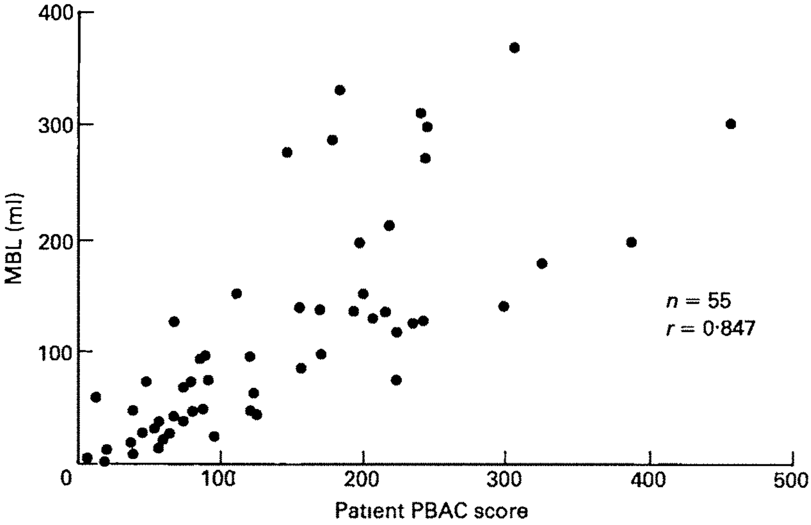

Fig. 2. Pictorial blood loss assessment chart (PBAC) score recorded by the woman against measured menstrual blood loss (MBL).

between the score recorded by the gynaecologist and the measured blood loss is shown in Figure 3. Both plots indicate that there was an increasing spread of the results at higher levels of blood loss; this variability was greater for the scores recorded by the women. A Spearman ranked correlation coefficient is quoted for each plot. The agreement between the scores recorded by the gynaecologist and the patient is shown in Figure 4. This plot of the differences between the scores against the mean shows reasonable agreement with scores of <150, thereafter the magnitude of the differences increases and exceeds 2 SD of the differences.

Approximately half the cycles monitored showed a blood loss of >80 ml by the alkaline haematin method. Taking a score of ≥100 as diagnostic of such menorrhagia, the pictorial

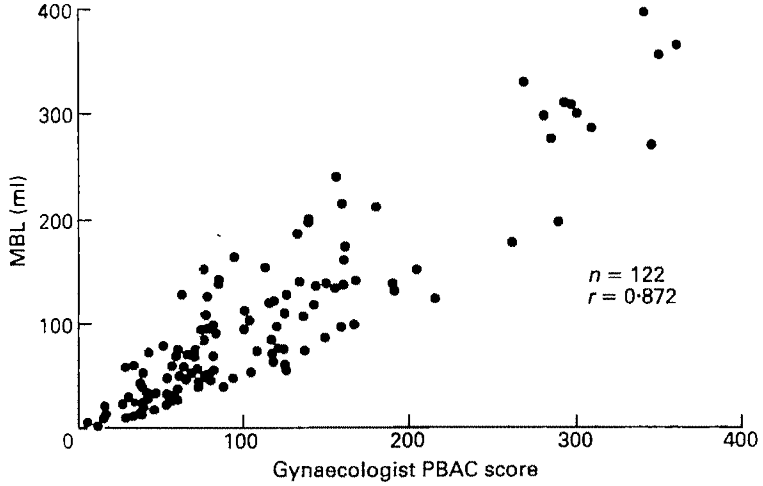

Fig. 3. Pictorial blood loss assessment chart (PBAC) score recorded by the gynaecologist against measured menstrual blood loss (MBL).

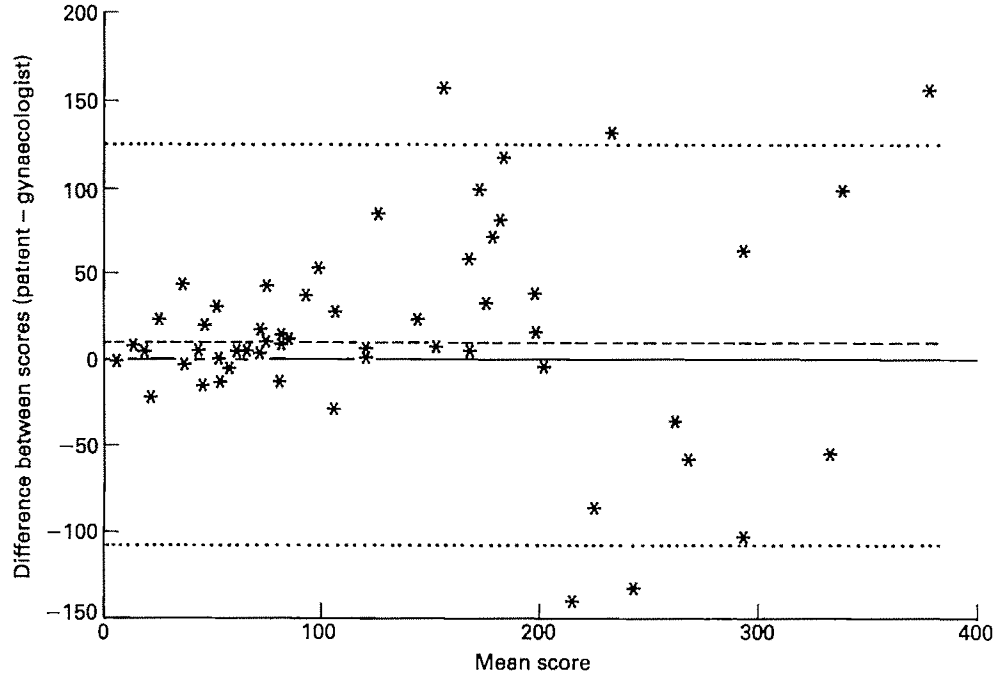

Fig. 4. Difference between patient and gynaecologist in recorded pictorial chart score against mean score

method was found to have a sensitivity of 86% and a specificity of 89%, using the scores recorded by the women. The sensitivity and specificity were 86% and 81%, respectively, using the gynaecologist's scores.

In the group of 122 monitored cycles, a positive correlation was found ($r = 0{\cdot}74$) between the total number of sanitary towels and tampons used and menstrual blood loss in ml (Figure 5).

Discussion

We have demonstrated that there is a relation between the standard alkaline haematin method of menstrual blood loss determination and the pictorial blood assessment chart scores from both patients and a gynaecologist. There was good acceptance of the pictorial method and, with only two exceptions, the patients found the charts easy to use. Women apparently have quite an accurate perception of the degree to which their sanitary towels or tampons are soiled over a wide range of menstrual losses The extent to which items are allowed to become soiled is partly determined by the rate of blood flow, but the tolerance of heavily soaked items varies considerably. In this particular study, the women who bled more did tend to use a greater number of sanitary items, but the fallibility of relying on the towel or tampon count alone is easily demonstrated. For example, one woman managed to collect 399 ml on just 18 towels and another used the same number of towels for a menstrual loss of 32 ml. Using the pictorial chart will help to discriminate between such individuals.

Taking account of the passage of clots (especially those of larger size) by a separate score added to the pictorial chart score was important in the assessment of those patients with a menstrual loss of >80 ml. This factor could not be assessed in the same manner by the gynaecologist and, in some instances, may account for the poorer agreement between gynaecologist and patient scores at higher values. In the plots of pictorial chart score versus measured menstrual blood loss, there is an increasing scatter as blood volume increases. This may be partly explained by the fact that towels and tampons appear similar, even though they may have absorbed different quantities of blood.

The five women who had complained of menorrhagia and were found to have menstrual blood loss well within the normal range (<80 ml) did appear to recognize the fact that towels and tampons were only lightly or moderately soiled with blood. For some women simple reassurance

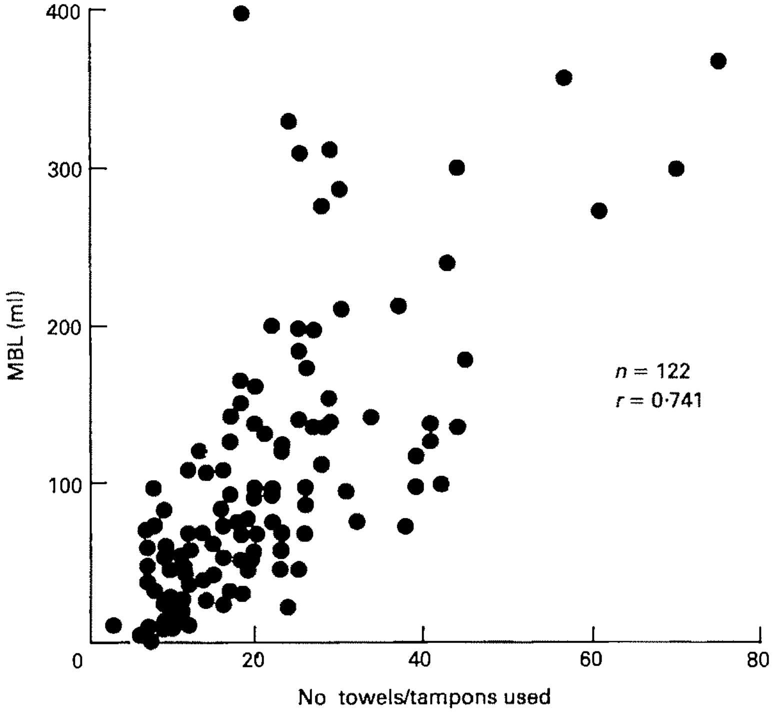

Fig. 5. Number of sanitary items used against measured menstrual blood loss (MBL).

that their menstrual blood loss appears normal (substantiated by a low pictorial chart score) is sufficient to dissuade them from embarking on a course of unnecessary treatment.

It is likely that in our study the accuracy of the pictorial chart assessment was increased because most of the women used only the towels and tampons supplied for the trial which were approximately uniform in size and absorbency. This is possible in a clinical trial, but the wide variety of sanitary protection available on the retail market may limit the accuracy of the method for general use The capacity to absorb blood varies widely between a mini and super-plus tampon; further assessment of the influence of the size and type of sanitary protection is necessary (Grimes 1979).

Falsification of a pictorial chart assessment would be easy, but the option of asking the woman to collect her sanitary material for inspection, would remain for the sufficiently motivated clinician.

The pictorial blood assessment chart could also have a role in monitoring treatment of menorrhagia Once a baseline score has been established, subsequent treatment cycles can be assessed in the same way and success indicated by a decreasing score. This method could be of value to both clinical practitioner and research worker who have no facility to assess menstrual blood loss objectively. In conclusion, although the pictorial method of assessing menstrual blood loss is not as accurate as objective measurement, it provides a simple and useful adjunct to enable the clinician to discriminate between those women who require treatment and those who should be dissuaded from it. This may avoid unnecessary drug therapy, hospital referral and even surgical intervention in a significant proportion of women.

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SHORT COMMUNICATIONS

Maternal abdominal pressure alters fetal cerebral blood flow

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The aim of this study was to examine systematically the effect of fetal head compression caused by the ultrasound transducer on flow velocity waveforms from the middle cerebral and internal carotid arteries.

The study included 45 women with uncomplicated singleton pregnancies recruited from the routine antenatal clinic at 26, 32 or 36 weeks gestation. There were 15 women in each gestational age group and these were subdividied into three groups of women to study each of three fetal vessels (middle cerebral artery, internal carotid artery and thoracic aorta).

Colour flow imaging (Acuson 128, 3·5 MHz sector transducer, high pass filter 125 Hz) was used to identify the proximal portion of the middle cerebral artery, the intracranial portion of the internal carotid artery, or the descending thoracic aorta. The pulsed Doppler range gate was then placed on the appropriate vessel and all flow velocity waveforms (FVW) were obtained in the absence of gross fetal body or breathing movements. When three waveform recordings of satisfactory quality had been obtained, the maximum frequency envelope was outlined with a light pen and the pulsatility index (PI) of each FVW determined (spectrum analyser, Doptek Spectrascan 9000, UK). The intensity weighted time averaged mean blood velocity was computed for waveforms from the middle cerebral artery. The average of three values was calcu-

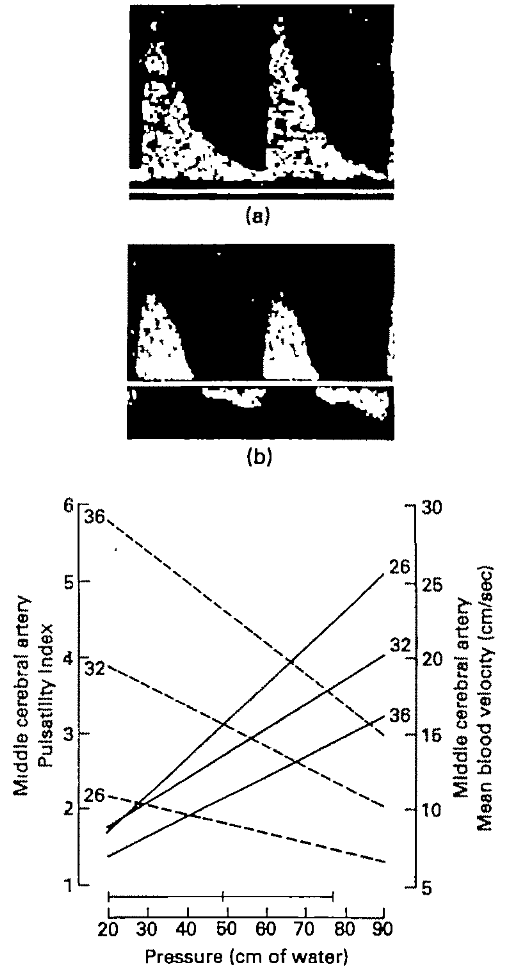

Fig. 1. Flow velocity waveforms from the middle cerebral artery during minimal head compression demonstrating the presence of end-diastolic frequencies, 30 cm H_2O (a) and, when more pressure is applied, there is reversal of end diastolic frequencies, 70 cm H_2O (b). The regression lines demonstrate the increase in pulsatility index (——) and decrease in mean blood velocity (---) with increasing degrees of pressure at 26, 32 and 36 weeks gestation. The horizontal bar represents the mean ± 2 standard deviations of pressure exerted during imaging of the biparietal view

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Table 1. The relation of fetal heart rate (FHR) and mean blood velocity (MBV) or pulsatility index (PI) in the fetal circulation and pressure applied to the maternal abdomen

Gestation (weeks)	Vessel	Pressure (cm of water) Mean (SD)	Correlation with pressure (r) FHR	PI	MBV
26	MCA	52·1 (19·4)	−0·15	0·64†	−0 48*
26	ICA	50·8 (18·2)	0·08	0·74†	—
26	AOR	44·8 (13·6)	−0·16	0·46	—
32	MCA	61·2 (19·1)	−0·15	0·65†	−0·52*
32	ICA	55·9 (18·9)	−0·30	0·75†	—
32	AOR	49·0 (16·6)	−0·05	−0·11	—
36	MCA	58·1 (20·6)	−0·24	0·62*	−0·78†
36	ICA	60·7 (17·5)	−0·28	0·38	—
36	AOR	47·4 (14·4)	0·09	0·01	—

MCA = middle cerebral artery; ICA = internal carotid artery; AOR = descending thoracic aorta. * = $P<0·05$, † = $P<0·01$.

lated. In each subgroup of five patients three degrees of increasing pressure were applied to the maternal abdomen by the ultrasound transducer and the fetal heart rate and FVW characteristics were recorded.

The pressure exerted by the transducer was measured by an open ended water filled manometer whose reservoir was contained in a plastic bag. The latter was placed on the maternal abdomen and the height of the vertical column of water (in cm) in the manometer arm was measured. All imaging and Doppler studies were performed by using the reservoir bag as an 'offset'. Thus, the pressure being exerted on the maternal abdomen (through the bag) caused an increase in the height of the vertical column of water in the manometer arm.

The mean pressure exerted by the transducer during routine measurement of the fetal biparental diameter in 15 women having this examination was 49 cm of water (SD 14·5, range 22–77). The mean pressure during the Doppler studies was 54 cm of water (range 20–94).

The relations between the pressure applied and the Doppler measurements are shown in Table 1. There were significant positive correlations between pressure exerted and the PI of FVWs from the internal carotid and middle cerebral arteries but not the aorta. Furthermore, the mean blood velocity in the middle cerebral artery decreased (Fig. 1). In the FVWs from the middle cerebral and internal carotid arteries, increasing pressure was associated with loss of end diastolic frequencies in nine and six examinations respectively; in addition, there was reverse flow in six and two examinations respectively. The fetal heart rate did not change significantly during these studies (Table 1).

Discussion

The fetal brain is a readily compressible structure contained within a confined space. The application of external pressure must result in an increase in the intracranial pressure which should lead to a rise in impedence to flow within the cerebral circulation. Furthermore, the significant fall of mean blood velocity in the middle cerebral artery indicates that an increase in maternal abdominal pressure could result in a reduction in fetal cerebral perfusion, as it must be assumed that the diameter of the vessel would not be altered. In contrast, fetal thoracic compression by the transducer is not associated with alteration of the aortic FVW, presumably because intrathoracic pressure is not raised.

The most likely explanation for the more pronounced effect on the middle cerebral artery than the internal carotid artery is that the latter is further from the site of the application of pressure; pressure falls as a function of the square of the distance from its origin. With advancing gestation maternal abdominal compression has a lesser effect on the FVWs from fetal intracranial vessels; this may be due to the increased rigidity of both the fetal brain and skull.

Since intrauterine growth retardation is associated with oligohydramnios and consequent difficulty in imaging, care should be taken to minimize compression of the fetal head during Doppler studies of the intracranial circulation.

Indeed, undue compression of the fetal head by the ultrasound transducer may be the cause of the reported high impedence to flow in the internal carotid artery of fetuses with renal agenesis and associated anhydramnios (van den Wijngaard *et al.* 1988). In fetal hypoxia the expected redistribution of blood flow in favour of the brain would be associated with decreased impedence to flow or increased blood velocity. The findings of this study show that minimal transducer pressure should be exerted during Doppler examination of the fetal head to avoid an artefactual increase in impedence to blood flow, and thus, a high false negative rate in the detection of fetal hypoxia.

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The histochemistry of oestradiol-17β dehydrogenase in normal endometrium and endometrial carcinoma: A test to predict the sensitivity of endometrial carcinoma to progestogens: A preliminary report

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Progestogens have been used to treat endometrial carcinoma for nearly 40 years (Kelley 1951). Their major advantage is a lack of serious adverse effects, but unfortunately not all tumours will respond (Kneale *et al.* 1982). This has prompted a search for a reliable method of predicting whether a given tumour will be sensitive to progestogen therapy.

Although there is a relation between tumour response and both histological differentiation (Kohorn 1976) and progesterone receptor status (Ehrlich *et al.* 1981), both methods have been found too imprecise for routine use (Podratz *et al.* 1985; Kneale 1986). Elevations in the activity of oestradiol-17β dehydrogenase have previously been used as an index of progestogen potency in normal endometrium (Whitehead *et al.* 1981) and this enzyme has also been suggested as an indicator of the progestogen sensitivity of endometrial carcinoma (Gurpide & Tseng 1978; Pollow *et al.* 1980). Increases in enzyme activity in response to progestogen treatment imply that not only are appropriate intracellular steroid receptors present but also that post-receptor pathways exist that allow the hormone to exert its effect.

We measured oestradiol-17β dehydrogenase activity histochemically and biochemically in the endometrium of 26 apparently healthy postmenopausal women. Endometrial biopsies were obtained at various times during therapy either with oestrogen alone or in combination with a progestogen. Endometrium was also obtained from eight women with endometrial carcinoma. Four women were given oral medroxyprogesterone acetate (MPA) (Provera; Upjohn Ltd) 200 mg daily for 7 days immediately before surgery.

Frozen sections of 25 μm thickness were cut and the technique of Morse and Heller (1973) was modified (Lane 1989) to display the histochemical activity of oestradiol-17β dehydrogenase without prior knowledge of the patient's therapy. The overall colour reaction was esti-

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mated as follows: 0 = no reaction product; + = little reaction product; ++ = moderate reaction product.

The biochemical activity of endometrial oestradiol dehydrogenase was measured in the supernatant following tissue homogenisation (King *et al.* 1981*a*).

Results and discussion

All but one of the endometria obtained from postmenopausal women were normal. The other specimen, obtained on day 3 of combined therapy with oestrogen and progestogen, contained areas of atypical hyperplasia. Neither this latter specimen nor any of the normal endometria from women in the oestrogen-only phase of therapy exhibited either biochemical or histochemical evidence of oestradiol dehydrogenase activity. Normal endometria from women treated with both oestrogens and progestogens exhibited biochemical activity. All these specimens also showed histochemical evidence of enzyme activity, which produced only light or moderate staining (Fig. 1).

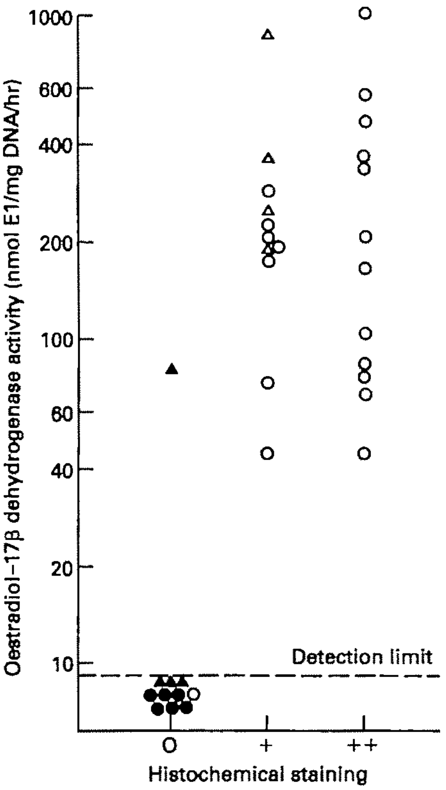

Fig. 1. Relation of histochemical and biochemical activities of oestradiol-17β dehydrogenase in normal endometrium from patients treated with oestrogen alone (●), or oestrogen and progestogen (○) and both MPA-treated (△) and untreated (▲) endometrial carcinomata. 0 = no histochemical staining, + = light staining, ++ = moderate staining.

Oestradiol dehydrogenase activity was present biochemically in the homogenates of all MPA-treated tumours and the enzyme was visible histochemically within malignant epithelium in all these specimens (Fig. 1). Three of the four untreated tumours exhibited neither biochemical nor histochemical enzyme activity. The fourth specimen demonstrated a relatively low level of biochemical activity (79·9 nmol oestrone mg DNA^{-1}h^{-1}) which was not visible histochemically (Fig. 1).

In both benign and malignant specimens, oestradiol dehydrogenase activity was located within the epithelium whilst all stromal elements remained unstained. This confirms the biochemical observations of our group (King *et al.* 1981*b*) on separated epithelium and stroma and a previous histochemical study (Scublinsky *et al.* 1976).

In both benign and malignant specimens some glands were strained whilst others were not. This heterogeneity is particularly important in endometrial carcinomata where, if a wide variation in response exists between different areas, the tumour might be less sensitive to progestogens than analysis of the whole tissue would imply.

Although there was no significant relation between the biochemical and histochemical assessment of enzyme activity (Fig. 1) (Wilcoxon rank sum test $P>0{\cdot}05$), histochemical assessment of oestradiol dehydrogenase activity may have advantages over the biochemical methodology. Both techniques seem equally sensitive, but radioactive isotopes, essential for the biochemical methodology (King *et al.* 1981*a*), are not necessary for the histochemical technique, which may also display heterogeneity within the tissue. Consequently we suggest that the histochemical technique for measuring oestradiol-17β dehydrogenase activity in endometrium to predict the sensitivity of endometrial carcinoma to progestogens is worthy of further study.

Acknowledgments

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The selection of capillary tube diameter for fetal scalp blood sampling

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Fetal scalp blood sampling needs experience, correct technique and appropriate equipment. Occasionally a high presenting part or inade-

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quate cervical dilatation may cause difficulty and then technique and type of equipment may decide success or failure. Blood may be allowed to enter the collection tubes passively or by suction. Suction frequently draws in air, breaking the blood column, and is also hazardous if done by mouth, even with an intervening plastic tube.

In a study on fetal scalp blood sampling in low risk labour (Ingemarsson & Arulkumaran 1986) capillary tubes with different internal diameters were used. Tubes with smaller internal diameters filled most readily, suggesting that surface tension was an important factor in tube filling. Provided the blood 'wets' the inside of the tube, the meniscus generates a 'suction' pressure in the fluid column. This pressure is expressed by the formula 2T/r, where T is the surface tension of the blood and r the internal radius of the tube. Thus the greater the blood's surface tension, and the smaller the inner radius the greater is the negative pressure drawing fluid into the tube. The surface tension of aqueous solutions usually increases with increasing solute concentration (Kaye & Laby 1982) but is decreased by surface active agents. The surface tension of fetal blood has not been reported and so we decided to measure the pressure experimentally.

The volume of the blood sample required for acid base analysis varies with the make of the automatic blood gas analyzer and whether measurement is made on the manual or automatic mode. For a given volume, the smaller the radius, the longer is the required column of blood. We have investigated the influence of the diameters of the capillary tube on the size of the fetal blood sample and the compatibility of the tubes with various blood gas analyzers' ports, as some will not accept the smaller diameter capillary tubes.

Methods and materials

The flow inducing pressure generated by surface tension was measured by the 'capillary rise' method. When a clean tube is held vertically with its lower end immersed in the fluid, the fluid rises in the tube until the weight of the fluid column balances the upward force due to surface tension. The height is measured, and multiplied by the fluid density to give the pressure it is exerting to balance the surface tension forces. With heparinized fetal blood, ascent was usually complete within a few seconds but a standard settling time of 30 s was allowed. The tube was then slowly lifted, still vertical, out of the fluid. The meniscus remains at a constant height above the free surface as the tube is raised until the lower end of the tube breaks clear at the surface. The fluid column then remains in the tube to give a record of the height attained. The tube was laid in a slightly sloping rack to avoid it travelling up the tube and its length measured to the nearest mm with a scale.

Before the experiment, the internal diameter of the capillary tubes was measured by a travelling microscope with vernier scale to make sure that the tubes had reasonably paralleled lumens and were in accordance with the manufacturer's description of tube diameter. Our samples were reasonably parallel judged by observing the height of the fluid column while raising and lowering the tube in the fluid container. Measurements of the column of fluid as described was made for distilled water and heparinized fetal blood collected from the umbilical cord vein at delivery with tubes of four different internal diameters (0·58, 0·69, 0·86 and 1·25 mm). The experiment was repeated to calculate the mean length of the column from 30 tubes of each diameter.

The second part of the experiment was to verify whether the different diameter tubes would fit into the ports of the different machines. Heparinized fetal blood was taken into 10 tubes of each diameter for this experiment.

Results

The height of the blood column was always less than that of water. The internal diameters of the tubes and the typical rise in each size of tube are shown in Table 1. For ease of discussion results are expressed in terms of the pressure exerted by a column of water or fetal blood H cm in height.

Table 2 provides information about the minimum blood volume needed for the different automatic blood gas analyzers for blood gas analysis and the minimum length of blood column needed with each diameter tube. The Corometrics 220 pH machine, although needing only 15 µl of blood, would not accept the narrowest capillaries (0·58, 0·69 and 0·86 mm internal diameters). The capillary with 0·58 mm internal diameter could not be used with any of the machines because of incompatibility with the port size.

Table 1. Height of water and fetal blood columns in relation to capillary tube internal diameter

Inernal diameter of tubes (mm)*	Mean height of 30 fluid columns (cm) Water	Fetal blood
0·58	6·50 (0 47)	5·90 (0·13)
0·69	4·53 (0·18)	3·88 (0·21)
0·86	3·59 (0·10)	2·93 (0·27)
1·25	2·21 (0·03)	2·18 (0·14)

Standard deviations are given in parentheses.
*0·58, 0·69 & 0·86 mm tubes—Intracel Ltd., Royston, Herts, UK
1·25 mm tubes—Radiometer A/S, Copenhagen, Denmark

Discussion

The drop of blood that one is trying to induce to enter the fetal scalp blood sampling tube is at rest supported by its own surface tension and will stay immobile until that surface tension is broken or other forces act. When the glass tube makes contact with the drop, wetting of the surface results in a change from convex, in which tension holds the blood back into a droplet, to concave in the tube, thus pulling the blood in. Gravity tends to make the blood drop off the end of the tube and is no help at this stage. Thus the ease of initial entry is largely independent of the angle at which the tube is held. Later once a partial column has developed, causing the tube to slope down away from the scalp may help filling by gravitational forces but the resulting increase in induction pressure will generally be less than half that contributed by surface tension, even when the column is nearing its maximum required volume. If the tube is inclined at 30°, probably the maximum practical within the amnioscope, the effective column height is only half (Sin 30°) the column length. For example when a 0·69 mm tube was held vertically in fetal blood the column height was nearly 40 mm (Table 1). The additional assistance to be obtained from gravity if this tube is inclined downwards at an angle of 30° is only 2·0 cm blood, about half of the pressure continuously exerted by surface tension. Passive filling is thus principally dependent on surface tension forces. The rate of initial filling of the tube depends on the spreading rate of the film of fluid rather than viscosity. This can be observed by noting the initial rate of rise, tilting the tube to allow it to fill further and restoring it to the vertical. The rate of fall with the tube internal surface already wetted is very much faster than the initial rise. We were unable to find data on the factors controlling rate of spread of a blood film.

In a labour ward with AVL 939 or 940 blood gas analyzer, a blood column of 6·6 cm in a tube with an internal diameter of 0·69 mm (25 µl) would be sufficient for a blood gas analysis by the manual mode whereas a column of 10·7 cm (40 µl) is needed for the automatic mode. With the same diameter tube, a column of 10·7 cm (40 µl) is needed for the 'split' or manual method with a Corning 178 blood gas analyzer, whereas a column of 22·7 cm (85 µl) is needed for the analysis on the automatic mode. Most narrow capillaries are made with a maximal length of 15 cm. For the Radiometer ABL 330, 85 µl of blood and for the ABL 30, 125 µl of blood are needed which makes it necessary to use a larger diameter capillary tube. Use of a capillary with internal diameters of 0·69 or 0·86 mm with a

Table 2. Length of the column of blood (in cm) needed for blood gas analysis related to internal diameter of tube and type of blood gas analyzer

	Length of blood column needed (cm)* AVL 939/940	Radiometer ABL 30	ABL 330	Corning 178
Internal diameter of tube (mm)				
0·69	6·6 (10·7)	33·4	22·7	10·7 (22·7)
0·86	4·3 (6·8)	21·5	14·6	6·8 (14·6)
1·25	2·0 (3·2)	10·1	6·9	3·2 (6·9)
Volume needed for analysis (µl)	25 (40)	125	85	40 (85)

*The length of blood column needed with some capillary tubes is >15 cm but the maximum capillary length generally available and easily handled is 15 cm
The number in parenthesis indicates the length or volume of blood column required for automated mode of analysis.

machine which can perform the analysis with 25 or 40 µl of blood should help to avoid frustration during fetal scalp blood sampling.

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BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting on 3 September 1989 at the University of Southampton

A placebo controlled study of an anovulatory dose of oestradiol patches and cyclical oral norethisterone in the treatment of premenstrual syndrome by N. R. Watson, T. G. Garnett, M. Savvas, R. Baber & J. W. W. Studd. The Pre-Menstrual Tension Clinic, Dulwich Hospital, East Dulwich Grove, London SE22 8PT.

Premenstrual syndrome as defined by statistically significant ($P<0{\cdot}05$) positive and negative symptom trends in daily Moos Menstrual Distress Symptoms (MDQ) ratings was confirmed in 40 women. They were randomly allocated to receive placebo or active treatment with 200 μg transdermal oestradiol patches and norethisterone 5 mg from days 21 to 28 of each 28-day cycle for 3 months, treatment was then crossed over and continued for a further 3 months. Both groups were matched for age, marital status, parity, duration of premenstrual syndrome and duration of the Premenstrual Distress Questionnaire (PDQ) for the duration of the study. Five women withdrew from the study, four because of skin reactions and one because she felt so much better and wished to continue on her initial therapy. Analysis of data showed an initial placebo response which was no longer statistically significant at 3 months. There was a significant improvement in all six DQ symptom clusters with active compared to placebo treatment. Analysis of the 10 PDQ questions showed significant improvements with non-parametric statistical tests in concentration, tiredness, tension, depression, loss of efficiency, irritability, mood swings and feelings of bloatedness. There was no significant improvement for restlessness or weight gain. This study shows that suppression of ovulation with percutaneous oestradiol patches is an effective treatment for the premenstrual syndrome.

Metabolic and endocrine findings in AGA and SGA fetuses by D. L. Economidès & K. H. Nicolaides. Harris Birthright Centre, Kings College Hospital, London.

In order to investigate the metabolism of appropriate (AGA) and small (SGA) for gestational age fetuses, blood gases and pH, blood glucose, lactate, plasma triglycerides, non-esterified fatty acids (NEFA), glycerol, 21 amino acids and plasma insulin were measured in blood samples obtained by cordocentesis at 17 to 38 weeks gestation. In AGA fetuses, blood PO_2 and pH decreased, PCO_2 increased and lactate did not change with advancing gestation. Plasma insulin and the insulin-to-glucose ratio increased with gestation reflecting the progressive maturation of the pancreas. Plasma triglyceride concentrations decreased with advancing gestation, presumably a consequence of fat deposition. Fetal plasma amino acids were higher than, but correlated with, maternal levels, indicating that they are actively transported by the placenta. In SGA fetuses there was umbilical venous and arterial hypoxaemia, hypercapnia, hyperlacticaemia and acidosis. There was also fetal hypoglycaemia and the materno-fetal glucose gradient was increased. There was hypoinsulinaemia and low insulin-to-glucose ratio, indicating that there may also be pancreatic dysfunction. Plasma triglycerides were elevated, a consequence of reduced utilization of triglycerides for oxidation or fat deposition. In fetal hypoxaemia the fetal plasma ratio of non-essential-to-essential amino acids was increased suggesting that in growth retardation, intrauterine starvation occurs.

Computerized spectral analysis of heart rate variability in high risk pregnancy by P. Fogarty & J. C. Dornan. Royal Maternity Hospital, Belfast, N. Ireland BT12 6BB.

The accurate diagnosis of fetal distress remains difficult with misdiagnosis having significant consequences for the infant, the mother and her attendants. More precise methods are required.

Using a locally developed on-line microprocessor-based system, spectral analysis of the fetal ECG has been performed (normal reference range presented to the Blair Bell Research Society, September 1987). We have now performed spectral analysis on a large number of high-risk pregnancies. Of particular interest are two groups of patients, those undergoing emergency caesarean section for fetal distress and infants born with birth asphyxia. We have related the spectral analysis of the ECG to the clinical condition, Apgar score and cord artery pH of the infants at delivery. This technique provides an objective and relatively non-invasive method to detect genuine fetal compromise. The results are extremely encouraging and they will be presented in full.

Serum CA 125 and prediction of outcome in ovarian cancer by C. W. E. Redman, G. R. P. Blackledge, E. J. Buxton, F. G. Lawton & D. M. Luesley. West Midlands CRC Clinical Trials Unit, Birmingham, UK.

Despite the advent of active chemotherapy in epithelial ovarian cancer (EOC), not all patients respond to treatment and in some responding patients the duration of response is short-lived, failing to justify the toxicity and disruption in the quality of life that such treatment can entail. The monitoring and assessment of response in EOC can be difficult, but serum CA 125 may facilitate an early appraisal of response and identify those patients unlikely to derive benefit from continued intensive chemotherapy. Serum CA 125 levels were measured in 50 EOC patients, receiving first-time *Cis*-platinum based chemotherapy, before treatment and after two cycles of treatment. Subject to response (assessed by UICC criteria) and toxicity, patients received up to eight courses of treatment. The overall response rate was 76% and median survival for the group was 16·4 (95%CI 9·8–23·0) months. Median time on-study was 25 (95%CI 23–25) months; range 14–32 months. An initial univariate analysis of prognostic variables, including serum CA 125 levels before treatment and after two courses, and percentage fall in serum CA 125 levels was performed In this analysis a cut-off point of 30 U/ml for CA 125 values, and multiple cut-off points (25–90) for percentage fall were used. On the basis of this analysis, residual disease, and serum CA 125, both before treatment and after two courses, were significant prognostic variables, of which the second serum CA 125 value was the most important. Patients with a second serum CA 125<30U/ml were more likely to achieve a complete remission (χ^2_1 17·8; $P<0·0001$) and survived significantly longer (χ^2_1 11·1; $P=0·0009$) than patients with elevated levels. Because of the potential interaction of these and other factors, a stepwise discriminant analysis was performed using survival at 12 months after primary surgery as the end point. Serum CA 125 ($\log_e$ transformed) after two courses of treatment gave the greatest discrimination between patients who were alive or dead at 12 months. No other variables could significantly improve predictive accuracy. Using the classification function derived from this analysis, it was possible to correctly predict 85% of patients who would be dead at 12 months, and 96% of survivors (an overall predictive accuracy of 93%). These results indicate that serum CA 125 levels after only two courses of treatment can identify good and poor prognostic groups of patients enabling timely and appropriate changes in treatment strategy.

The sodium pump in hypertensive pregnancy: is it inhibited? by S. Macphail, T. Thomas, R. Wilkinson, J. M. Davison, W. Dunlop. Departments of Obstetrics and Nephrology, University of Newcastle upon Tyne.

Sodium pump inhibition has been suggested as one possible cause of essential hypertension. The pump can be inhibited by the cardiac glycosides such as digoxin and it happens that the serum of pregnant women contains a digoxin-like immunoreactive substance (DLIS) which may be further increased in hypertensive pregnancy. This raises the question of whether inhibition of the sodium pump plays a role in the pathophysiology of pregnancy-induced hypertension (PIH) We have assessed parameters of sodium pump kinetics in 30 normotensive (NT) and 30 hypertensive (PIH) primigravidae and a non-pregnant control group ($n=10$). We have measured intracellular sodium content ([Na]i) and the available activity of the pump (k_0) under *in vivo* conditions; maximum velocity of the pump (Vmax) and the k_{Na}, a measure of its affinity for sodium, were measured under *in vitro* conditions. The results are shown in the following Table.

Intracellular sodium content was decreased equally in both hypertensive and normotensive

	[Na]i (mmol/kg)	$k_{o\text{-}1}$ (h)	k_{Vi} (mmol/kg)	Vmax (mmol/kg/h)
Controls	5·01†	0·35†	3·12	7·51
NT	4·04†	0·45†	2·60	9·13*
HT	4·03	0 47	2·38	8·03*

*$P<0·05$, †$P<0·01$

pregnancy with an increase in the k_o and Vmax. If the pump were inhibited [Na]i would rise as sodium was prevented from leaving the cell and as more pump sites were recruited, in an attempt to reduce [Na]i, the Vmax would increase. These results would suggest that sodium pump inhibition does not play a role in the pathophysiology of pregnancy induced hypertension.

The assessment of fetal growth in multiple pregnancy by M. A. MacLean, A. M. Mathers, J. J. Walker, A. D. Cameron, R. C. L. Howat & J. R. MacKenzie. Glasgow Royal Maternity Hospital, Rottenrow, Glasgow G4 0NA.

A Twins Clinic was established in GRMH in 1983 in an attempt to reduce the perinatal mortality and morbidity. Serial symphyseal fundal height (SFH) measurements using a centimetre tape, and ultrasound examinations are used in the assessment of growth. Each pregnancy is scanned at intervals of 4–6 weeks until 28 weeks and then every 2–3 weeks. The biparietal diameters (BPD) and abdominal circumferences (AC) are measured and the estimated fetal weight calculated from Campbell's tables using AC alone, and Warsof's tables using BPD and AC. A total of 130 pregnancies delivered after 28 weeks during 1984–1987 have been analysed. The aim of the study was to determine if SFH and/or ultrasound can detect discordant growth in twin pregnancies. Recordings at 32–34 weeks and at the last attendance before delivery were analysed. Discordance was calculated by dividing the weight of the smaller twin by the weight of the larger twin and expressing this as a percentage. The larger twin was used as a control. A significant degree of discordance was present if the percentage was <85%. There was a modest correlation between SFH and total fetal weight. Ultrasound estimation of total weight correlated well with total birthweight, but discordance was poorly detected.

What is the risk of open spina bifida in a woman with a raised serum alphafetoprotein but a normal ultrasound scan? by J. G. Thornton & R. G. Newcombe. The University of Wales College of Medicine, Cardiff CF4 4XN.

The risk of open spina bifida at a particular level of maternal serum alphafetoprotein (MSAFP) and after a negative ultrasound scan (US) depends on the prior population incidence, the level of MSAFP and the sensitivity of the US. The calculation is based on Bayes' theorem and involves sequential multiplication of odds. An adjustment also has to be made for the presumed non independence of MSAFP and US. Tables of risk at various population risks and MSAFP levels are available but there is none which incorporates US information. We have produced such tables and will distribute them at the meeting. The range of resulting risks is wide.

Example (a) An English woman (prior incidence 1 in 1000), MSAFP 5 MoM, negative 80% sensitive US. Final risk 1 in 10; (b) A woman from S. Wales (prior incidence 2 in 1000), MSAFP 2·5 MoM, negative 90% sensitive US. Final risk 1 in 730. We conclude that such tables should be used and the decision to offer amniocentesis individualized.

Using Lamicel before colposcopy to expose high cervical lesions by N. Johnson & A. C. Crompton. St James' University Hospital, Leeds.

The full paper has been published by N. Johnson *et al.* (*Br J Obstet Gynaecol* (1990) **97**, 46–52).

Genetic predisposition to eclampsia and severe preeclampsia by R. Arngrimsson, S. Bjórnsson, J. J. Walker, R. T. Geirsson & G. Snaedal. Department of Obstetrics and Gynaecology, National University Hospital, 101 Reykjavik, Iceland and University Department of Obstetrics and Gynaecology, Royal Infirmary, Glasgow G4 0NA, Scotland.

The full paper is in press: Arngrimsson *et al.* (*Br J Obstet Gynaecol* (1990) **97** in press).

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British Journal of Obstetrics and Gynaecology
August 1990, Vol. 97, pp. 751–753

CORRESPONDENCE

Survey of attitudes to testing for human immunodeficiency virus infection in antenatal clinics in West Glamorgan

Dear Sir,

The article by Dr Thomas *et al.* [*Br J Obstet Gynaecol* (1989) 1405–1409] concerning women's views about HIV testing in antenatal clinics suggests a far greater potential acceptability of this procedure than previous British studies. While the Swansea group reported that '94% had no objection to their antenatal blood specimen being tested', previous studies have reported uptakes of testing from 0·6% in Hackney to 74% in Riverside (Heath *et al.* 1988; Howard *et al.* 1989; Kransinski *et al.* 1988).

These differences may be due to different patient populations but we suspect that the amount and the type of advice given to women about the HIV test and the implications of its result are more important determinants.

The extent to which the way the HIV test is offered can affect its uptake is shown in a study from Philadelphia (Lendesman 1987) where different approaches for counselling antenatal patients were compared. In the first approach all were given a leaflet offering counselling about HIV testing, 30% accepted this offer of which subsequently 60% were tested (18% of the total). In the second approach, all attenders saw a counsellor who asked about risk factors and offered testing. This resulted in a 36% uptake rate. In the third approach all attenders saw a counsellor who discussed the dangers to the mother and baby without mentioning risk factors. This approach led to a 60% uptake rate. Conversely it could be argued that minimal counselling may also have the effect of maximizing the uptake rate of testing by failing to elaborate the disadvantages and implications of testing, but this approach would be undesirable in view of the possible adverse impact on the woman's mental health and social implications.

We believe that at present, the balance of evidence suggests that it is in the interests of the woman and her baby as well as her partner and the obstetric team to know the woman's HIV status. This should only be established, however, with the woman's consent.

We believe that we should be moving in the direction of offering HIV testing to all antenatal clinic attenders as a matter of routine, as it is clear from many studies that confining testing women known to be at risk leads to a large proportion of infected women being missed (45% and 83%) (Mendes *et al.* 1989; Stevens *et al.* 1989). However, the offer of routine testing for HIV needs to be done with care and sensitivity by well trained antenatal clinic staff to minimise the adverse consequences of HIV testing.

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Authors' reply

Dear Sir,

We would like to thank Dr Kell *et al.* for their comments on our report.

We agree that counselling is important, as our article indicated, but we believe the most important factor causing the regional variation in acceptability of HIV screening in antenatal clinics is the local prevalence of HIV infection. The women surveyed in West Glamorgan rightly perceived themselves to be at very low risk of infection.

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British Journal of Obstetrics and Gynaecology
August 1990, Vol. 97, pp. 752–753

Commentary: confidential enquiry into maternal death

Dear Sir,

Gibb's commentary [*Br J Obstet Gynaecol* (1990) **97**, 97–101] on the Department of Health (1989) report on maternal mortality includes a misleading statement on the relative mortality of elective caesarean section (CS) and vaginal birth: that the (direct) death rate after elective CS is about the same as after vaginal birth.

He does not explain how he ascertained mortality after vaginal birth, but I suspect that his miscalculation results from attribution of the deaths in early pregnancy and in undelivered women to the vaginal birth category. In fact, it can be ascertained from Table 1.5 in the Report that in women undergoing delivery there were 84 direct deaths, 43 indirect deaths, and 12 fortuitous deaths, totalling 139. The mode of delivery of these deaths is shown in Table 1 by type of death.

Table 1 Death after delivery by mode of delivery and type of death

	Mode of delivery		
Type of death	CS	Other (=vaginal)	Total
Direct	44	40	84
Indirect	20	23	43
Fortuitous	5	7	12
Total	69	70	139

The estimated number of vaginal deliveries (1 719 980) can be calculated by subtracting the estimated number of sections (185 820—from Table 12.2) from the number of maternities (1 905 800—from Table 1.7), thus allowing determination of the case fatality rate for vaginal births for comparison with that for elective and emergency CS (from Table 12.7). This comparison is shown in Table 2.

The differences between vaginal birth and elective CS are highly significant ($P<0{\cdot}001$). For all deaths, elective CS is 5·5 times more likely to result in death than vaginal birth, and for direct deaths only, 4·5 times more likely. As with emergency CS, the additional deaths should not of

Table 2 Deaths and case fatality rate per thousand by mode of delivery and type of death

	Mode of delivery		
	Vaginal (n=1719980)	Elective CS (n=86000)	Emergency CS (n=101000)
Direct deaths	40	8	36
(rate/1000)	(0·02)	(0·09)	(0·36)
All deaths	70	19	50
(rate/1000)	(0·04)	(0 22)	(0·50)

course be attributed solely to the operation, since some of the mothers have risk factors which predispose to CS and also to death. Nevertheless, Gibb's proposal that more sections should be done electively is open to question, and I consider that there is more wisdom in the statement in the Report (p.92): 'it is likely that any attempt to reduce the number (of emergency sections) by performing more elective sections would simply increase the overall CS rate'. It is worth noting that the Report documents two direct maternal deaths following elective CS where the indication for the CS was a previous CS.

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British Journal of Obstetrics and Gynaecology
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BOOK REVIEWS

Advances in Fetal Physiology: Reviews in Honor of G. C. Liggins (Research in Perinatal Medicine VIII), edited by: P. D. Gluckman, B. M. Johnston & P. W. Nathanielesz. Perinatology Press, Ithaca, New York, 1989, 424 pages, with figures and tables, $102

To obstetricians, the name Mont Liggins remains inextricably linked with maternal steroid administration for enhancing fetal lung maturity, one of the few obstetric interventions supported by recent meta-analyses. His discovery of the effect of glucocorticoids on pulmonary maturation was, however, made accidentally during some landmark experiments involving ACTH infusion in fetal sheep, into the role of the hypothalamo-pituitary-adrenal axis in the initiation of parturition. In the field of fetal physiology, he will be remembered for many other contributions including pioneering the chronically catheterized fetal sheep preparation, elucidating the role of fetal breathing movements in lung growth, and describing the physiological reflexes which permit pregnant seals to dive to depths of 500 metres for over an hour in freezing Antarctic waters with little change in fetal pH.

The diversity of his interests is reflected in the topics chosen for this *Festschrift*. Each plenary lecturer at Professor Liggins' retirement symposium in Rotorua in 1988 has produced not a transcript, but a comprehensive review of their area. Readers are thus spared the fragmentation and varying standard characteristic of most conference proceedings. Most topics in fetal physiology are covered authoritatively in this volume, which, given the paucity of texts in the field, deserves a place as a reference work.

Fetal physiologists have been accused of a preoccupation with 'measureable' phenomena such as fetal breathing and hormone levels. Although this book records the substantial knowledge acquired over the last two decades, we remain little closer to understanding the fundamental mechanisms involved in the onset of labour, in pulmonary hypoplasia after oligohydramnios, or to formulating potential therapies for growth retardation. Although there is little of immediate relevance here for the practising obstetrician, fetal medicine devotees currently delving into fetal physiology in the human would do well to familiarize themselves with this wealth of animal data before rediscovering the wheel.

Nicholas M Fisk

Assessment & Care of the Fetus. Physiological, Clinical and Medicolegal Principles, edited by Robert D. Eden and Frank H. Boehm. Prentice-Hall International Inc., (Appleton & Lange Connecticut,) 1990, 1043 pages, with figures and tables, £52.75

By bringing together in one book comprehensive reviews of fetal and maternal physiology and of the management of a wide range of obstetric problems, Eden and Boehm have given appropriate emphasis to the importance of basing clinical practice on a thorough understanding of physiological principles. The third section of the book is devoted to the processes involved in malpractice lawsuits and other medicolegal issues.

The 244 page section on physiological principles provides a systematic account of fetal, neonatal, placental and maternal physiology, which would be valuable reading for clinicians with an interest in perinatal medicine, and candidates for basic science examinations in obstetrics and gynaecology.

The section on clinical principles (673 pages) includes chapters on most diagnostic procedures relevant to clinical practice, and on the clinical management of important obstetric problems. The emphasis throughout is on defining the ranges of care which would be defensible in the event of litigation. While the need for preoccupation with legal liability has in the past been viewed as primarily relevant to practice in North America, changes in patterns of malpractice lawsuits are now causing concern in the United Kingdom and elsewhere. The possible impact of such concerns on the practice of medicine are difficult to overestimate. Litigation-consciousness must profoundly alter the nature of the relationship between the providers and the receivers of health care, as well as the nature of the care. Reference is made in the book to the lesser likelihood of litigation following aggressive than conservative management, and this must influence clinical judgement. Another important area is screening tests. When a laboratory test is used routinely in those with a very low risk of the condition, the anxiety produced by the testing and the chance of inappropriate management resulting from a false positive result may well outweigh the small chance of detecting an abnormality which would otherwise have been missed, and as a result being able to improve the outcome. Medicolegally, however, routine testing policies offer protection for the obstetrician.

Emphasis is placed on the assertion that medicolegally protective practice is 'usually' synonymous with good medical practice. It would have been of value had more discussion been included of situations in which this may not be the case, and of subtle ways in which medicolegal concerns may undermine practice.

Nevertheless, this book provides an authoritative obstetric reference text and a thoughtful approach to the medicolegal problems which increasingly face obstetricians and neonatologists.

G. Justus Hofmeyr

Principles and Practice of Clinical Gynaecology (Second Edition), edited by Nathan G. Kase, Alan B. Weingold, David M. Gershenson. Churchill Livingstone, New York, London 1990, 1065 pages with figures and tables, £60

Can a text book of 1078 pages, by 38 authors, meet the combined needs of three different audiences? This book aims, in one volume, to provide a reference source for medical students, residents in training, and established gynaecologists. It is certainly a comprehensive and authoritative account of modern American gynaecological practice.

The 58 chapters of the book are somewhat confusingly divided into eight parts, which are subdivided into between one and four sections. The parts on human reproduction and clinical gynaecologic endocrinology comprise more than one third of the book and, for many, will alone provide sufficient justification to purchase the book. These parts are quite outstanding but the sheer size and volume of information they contain will deter all but the most determined student. There is a good part on gynaecologic malignancies which should be of value to each of the target group. Part 4 is in different and clashing style. In its ten chapters, large areas of 'bread and butter' gynaecology are discussed under the heading of a cardinal sign of symptom. It may be helpful for those preparing for examinations to have a long list and brief discussions about numerous causes of a particular symptom, but to the more experienced readers, such a layout leads to much repetition and rather inappropriate juxtaposition of conditions. This student orientated section rather reduces the convenience of the book as a reference source.

This is an important book, which should find its place in every major gynaecological library. It is less certain that it will find a place in studies of individual students and junior doctors. It is a good book, which would be an even better one if it concentrated on what it really is, a major gynaecological reference work for those providing health care to women.

Ray Garry

Biopsy Pathology of the Endometrium by C. H. Buckley and H. Fox. Chapman and Hall Medical, London, 1989, 289 pages fully illustrated, £55

This, the fourteenth book in the Biopsy Pathology Series, maintains the high quality of its predecessors. The authors confine the text to diseases diagnosable on biopsies from the endometrium and discuss them in their usual direct, clear and concise way. The book is written with the surgical pathologist in mind, though gynaecologists will find it useful; there are lists of diagnostic features, differential diagnoses and histological features of prognostic importance. The chapters on the techniques and problems of endometrial sampling, the effects of hormones on the endometrium and the relation of pathology to prognosis of endometrial neoplasms will obviously be of use to clinicians as well as pathologists. The classification and pathology of endometrial hyperplasia and non-Müllerian endometrial neoplasms are particularly enlightening. With the increasing interest in gynaecological pathology and the improving cooperation between clinicians and pathologists this book will be widely welcomed.

D. G. Lowe

Maternal-Fetal Toxicology. A Clinicians Guide, edited by Gideon Koren. Marcel Dekker Inc., New York, Basel, 436 pages with figures and tables, $150 (US and Canada $125)

I have been using this book for reference more or less constantly since the review copy arrived.

It is a series of reviews of toxic effects of drugs, poisoning, radiation and occupational hazards. Effects on the mother, fetus, and newborn are considered. There is a chapter on drugs of choice for pregnancy, and a section on diagnosis of fetal malformations.

The final section describes the operation of Teratogen Information Services, and the 'mother risk' programme at the University of Toronto. The goals of the mother risk programme are: (1) To provide an authoritative information and consultation service to assist the pregnant patient or her physician in understanding fetal risks that may be associated with drug, chemical and radiation exposures during pregnancy, and (2) To develop and maintain an active research programme in the area of reproductive and developmental toxicology at the undergraduate, graduate and postgraduate levels.

Dr Koren and colleagues have produced a book which deserves great success—apart from library copies, I would recommend it to my colleagues as a 'bench book' to keep in antenatal clinics as an accessible source of information and sensible advice. Perhaps the publishers would consider a cheaper paperback edition.

I hope however, that the authors will accept *their* responsibility—having entered this field—to provide regular updates. This is the sort of information which might be easily transferred to and updated electronically.

R. B. Fraser

Books received some of which will be reviewed at a later date

Safer Childbirth? A Critical History of Maternity Care by Marjorie Tew. Chapman and Hall, London, 1990, 328 pages, paperback £14.95

The FIGO Manual of Human Reproduction. Three Volumes. Volume 1 Reproduction Physiology edited by Luigi Mastrianni, Jr & Christos Coutifaris, 150 pages illustrated. **Volume 2. Family Planning,** edited by M. F. Fathalla, A. Rosenfield & C. Indriso 220 pages illustrated. **Volume 3. Reproductive Health. Global Issues** edited by M. F. Fathalla, A. Rosenfield, C. Indriso, D. K. Sen & S S. Ratnam 250 pages illustrated. The Parthenon Publishing Group, Carnforth, Lancs, 1990, £19 per volume or £49 the boxed set

Otitis Media with Effusion in Children. The Dunedin Study (Clinics in Developmental Medicine No 108) by David Chalmers, Ian Stewart, Phil Silva & Anne Mulvena. Mac Keith Press, London, 1989, 167 pages with figures and tables £18.00

Modern Antenatal Care of the Fetus edited by Geoffrey Chamberlain. Blackwell Scientific Publications, Oxford, 1990 436 pages with figures and tables, £49.50

Contraception and Reproduction Health Consequences for Women and Children in the Developing World (Working Group on the Health Consequences of Contraceptive Use and Controlled Fertility) National Academy Press, Washington D.C. 1989, 118 pages, £12.85

Contraceptive Use and Controlled Fertility: Health Issues for Women and Children (Working Group on the Health Consequences of Contraceptive Use and Controlled Fertility) edited by Allan M. Parnell. National Academy Press, Washington D.C. 1989, 159 pages with tables, £15.55

Handbook of Drug Therapy in Reproductive Endocrinology and Infertility edited by Michel E. Rivlin. Little Brown and Company, Boston, Toronto, London, 1990, 256 pages illustrated, £16.50

Drugs in Pregnancy and Childbirth by Judy Priest. Pandora Press, London, 1990, 224 pages, £5.99 paperback

Baillière's Clinical Obstetrics and Gynaecology (Psychological Aspects of Obstetrics and Gynaecology Volume 3, No. 4 December 1989) edited by M. R. Oates Baillière Tindall, London, Philadelphia, 687–959 pages, single issue £18.50. Annual subscription UK £40.00 Europe £50.00

Prevention of Sexual Transmission of Human Immunodeficiency Virus (WHO AIDS Series 6). World Health Organization Geneva, 1990, 27 pages, Sw Fr 8.00

Miscarriage: Women's Experiences and Needs by Christine Moulder. Pandora Press, London, 1990, 254 pages £5.99

British Journal of Obstetrics and Gynaecology
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COMMENTARIES

Pain relief in labour

Queen Victoria herself was familiar enough with the pain of labour after the birth of her eighth child to pronounce chloroform analgesia a blessed relief. Somewhat nearer home my mother told me that after the birth of my eldest sister in 1926 she wept bitterly to think that she had brought into the world a girl who might one day herself have to endure such pain. She may have rationalized her puerperal depression which was possibly linked to that primordial instinctive desire of human beings to beget males, but she had no difficulty in remembering and conveying to me the severity of the pain she experienced with all her three non-interventional domiciliary deliveries.

Another memory of my teens in the early post war years was listening to a report on the wireless of a debate in the House of Commons in which the phrase was often repeated: 'Everything should be done to make childbirth as painless as possible'. With hindsight this must have presaged the Act of 1950 that permitted the use of pethidine by midwives.

Regional analgesia was first used in obstetrics at the turn of the century on the continent of Europe (Doughty 1987). In the 1960s continuous lumbar epidural analgesia was offered sporadically in labour in the UK, and by the end of that decade the then current generation of trendy women journalists began campaigning to make this technique more widely available. With the advent of bupivacaine this became feasible, the subspecialty of obstetric anaesthesia was born and every effort was made to improve the services nation wide. Then in the last decade the grassroots support for our efforts vanished.

This was the sequence of events in one country but similarities will be recognized wherever obstetric analgesia is practised. The lay public once acknowledged that labour was painful and wanted relief. Why, now that we are in a better position to relieve pain is its very existence so often denied?

The answer may lie in outcome. Though transmarginal inhibition may make us amnesic to stressful events, this effect is probably enhanced by the euphoria engendered at the birth of a live baby, whereas if a perinatal death (much commoner of yore) is the outcome, memory of the agony of labour and delivery may more often persist and hence be more widely acknowledged.

Now that we are in a position to relieve pain, I regret that women should ever be led to believe that labour is not particularly painful and as a result feel a sense of guilt and failure when they find that for them, like a majority of women, it is. In this issue of the Journal pp 789–796 a team from Uppsala (Gerdin and Cnattingius) present a detailed report on the use of obstetric analgesia in the whole of Sweden over a 4-year period. They found that, *inter alia*, very few parturients had no analgesia. As yet there has been no similarly detailed study of current practice in the UK as a whole, though one has been conducted this summer. There are, however, probably more similarities than differences between the Swedish and UK populations.

In my hospital most orthodox types of analgesia are freely available and the epidural rate is 40%. In an unpublished prospective survey of 106 women in their first pregnancy, 69% of those who expressed a preference said they intended to have no analgesia or only transcutaneous nerve stimulation (TENS) or Entonox, while only 12% intended to have epidural analgesia. In the event 3% had nothing, 14% TENS and/or Entonox and 60%, many of whom tried other methods first, finally opted for epidural blockade. This included 60% of those who intended to have minimalist analgesia. Expected pain and actual pain, measured by visual analogue scoring, did not differ significantly, however, suggesting that these women did not so much underestimate pain as underestimate their ability to tolerate it. Anaesthetic services to obstetrics should aim to take account of the woman's privilege to change her mind.

A survey of maternity facilities in the South

East Thames Region (Reynolds & Hanson 1990) showed that the epidural rate overall was 17%, similar to that in Sweden, but rates in individual units ranged from 0 to 40%. The hospital structure characteristic of the Swedish system does not exist here, though both countries (for the moment!) are blessed with a universally available health service that is free at the point of delivery. As in Sweden the epidural rate was more determined by the size of the unit and its staffing than by the ethnic mix of the population or other maternal factors apart from parity. The Swedish team surmized that the use of analgesia is determined at least in part by women's expectations. They are to a certain extent conditioned to require what they know to be available and this is certainly broadly true in the UK also. But is this the best reason for choosing a particular treatment? The anti-intervention lobby would deplore that a woman should be encouraged to have an epidural just because it is the norm in a particular unit. Their opponents, however, might say that epidural analgesia should be available to all, but is this correct? Well conducted epidural analgesia has advantages for the mother and even more so for the baby (Reynolds 1989) but an epidural poorly executed by an inadequately trained anaesthetist and badly maintained with imperfect back-up can be disastrous. It may be better to have no epidural service than one which is poorly supervised.

In Sweden 12% of women received paracervical block, a form of analgesia administered by obstetricians and hence available when an anaesthetist is not. Paracervical block became very popular in the 1960s (Cooper and Chassar Moir 1963; Gudgeon 1968; Hollmen *et al.* 1969), but the danger of fetal bradycardia and even intrapartum death (Nyirjesy *et al.* 1963; Yates *et al.* 1969; Asling *et al.* 1970), coupled with the increased popularity of epidural analgesia, led to its decline in the UK and USA. Another interesting aspect of Swedish practice is that midwives administer pudendal block. In Britain pudendal block has rather been the province of the obstetrician and moreover the skill has tended to die where epidural analgesia is common. A more versatile approach in the management of the second stage must surely be valuable.

The paper from Uppsala also implies that morphine, like pethidine, may be administered by midwives without prescription in Sweden, though the extent of its use is unspecified. In Britain pethidine is the only controlled drug in this category, while occasionally the less successful partial opioid agonists such as pentazocine (Refstad & Lindbaek 1980), metazinol (Nicholas & Robson 1982) and nalbuphine (Wilson *et al.* 1986) are used. That pethidine has pride of place is in part an accident of history in that when the decision came to allow midwives to give opioid analgesia without medical prescription it was the latest wonder drug. However, it is advantageous in that its onset of action is quicker than that of morphine, the latter being too lipid insoluble to penetrate the blood-brain barrier quickly. The newborn infant, of course, does not escape depression from any opiate agonist administered in labour and fetal accumulation is progressive with time (Reynolds & Knott 1989).

No mention is made of the use of TENS in Sweden. As a substitute for back-rubbing this technique has seen some popularity and it has the advantage shared by all types of patient controlled analgesia, of increased consumer satisfaction. Surprisingly enough, however, in controlled trials it has not been found to reduce the pain score or the need for supplementary analgesia (Harrison *et al.* 1986; Thomas *et al.* 1988).

In limiting their study to vaginal delivery Gerdin and Cnattingius have overlooked that most worrying group of women, those who are delivered by emergency section. General anaesthesia in these women is a conspicuous cause of maternal mortality (Department of Health 1989). It is in this category that the existence of an efficient epidural service is most valuable since it can with confidence be recommended to women at high risk and is in many ways preferable to general anaesthesia. A pre-existing effective epidural block can be extended for surgery in less time than it would take to prepare and position the woman, then to give 2-min preoxygenation, induce anaesthesia, wait for paralysis, pass laryngoscope and tube, inflate the cuff, connect and test it. General anaesthesia is by no means instantaneous.

In short there are medical as well as humanitarian reasons why epidural analgesia should be available to parturients, and they are summarized elsewhere (Reynolds 1989). Regrettably, though, an epidural service cannot economically and safely be provided in small maternity units.

If anyone reading this remembers experiencing a tolerable labour in which they coped with minimal or no analgesia they should remember that they are the exception rather than the rule. While we may envy and even admire such women we cannot expect that even given favourable circumstances the majority would be so fortunate. Many can bear witness that even for those who are perfectly calm, sensible, well informed, relaxed and unafraid labour can still be excruciatingly painful.

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Perinatal bereavement

It is only in the last 10 years that health professionals have turned their attention to the emotional needs of couples faced with a perinatal death. Ways of helping parents cope with their loss have been recommended (Health Education Council 1979) and Forrest *et al.* (1982) have demonstrated that the correct management of perinatal death reduces the frequency of prolonged emotional disturbance and of abnormal grief reactions. It is essential that every maternity unit should have a well planned policy for the management of perinatal death.

The principles of good management include correct medical treatment, effective communication, support and counselling, investigation of the cause of death, and in some situations, specialized counselling.

Communication is of particular relevance in perinatal death. Women clearly recall events surrounding the death. Most of the adverse comments regarding their management in hospital involve communication with medical and other members of hospital staff. Informing a couple of a death requires sensitivity and discretion. Explanations must be clear and unhurried; it may be necessary to repeat the information on one or more occasions. In this way, the trust and confidence of the couple will be gained. Trust is quickly destroyed by confusing or conflicting information. Both the hospital and community staff who are involved with the woman must be familiar with the facts surrounding the death and with the proposed management. Good communication requires good documentation. Listening is a part of communication which is particularly relevant during the grieving process.

It is important for the couple to talk to each other about their loss. Poor communication has been identified as a significant factor in marital break up following a perinatal death. Other children in a family, even if young, will be aware of a crisis. Parents must explain the situation in a simple and appropriate way. It is not uncommon for a child to have felt jealousy toward the unborn infant and to develop feelings of guilt after its death. Reassurance and the expression of extra affection are helpful in avoiding emotional problems in other children.

A woman will often find it easier to communicate with someone who has suffered a similar loss. Forrest *et al.* (1982) in a prospective randomized study showed that the provision of support and counselling is of significant benefit to a bereaved couple. In most instances, general supportive care and counselling by trained hospital and community staff is all that is required. Some knowledge of the nature, intensity and variation of the recognized stages of grieving is, however, necessary if staff are to provide a generally supportive approach to the couple (Lake *et al.* 1983).

Ways of facilitating the grieving process have been identified (HEC 1979; Lewis 1976). These practices include seeing and holding the dead baby, giving it a name and taking photographs; all help make the situation a reality and to create memories. It is very difficult to grieve when no memory of an individual exists. Seeing and holding the baby is important even if the baby is abnormal (Stierman 1987). This may upset the couple at the time but provides long term therapeutic benefit in coming to terms with the loss. Many women who do not see their baby later regret their decision and may report troublesome nightmares involving monsters. An adverse attitude to an abnormal baby by professional hospital staff may significantly affect the parents' response (Lovell 1983). The baby can be sensitively dressed so as to minimize the impact but disguising the abnormality may not always be the correct approach. Each situation should be judged on its own merits.

The perinatal death of a twin is a particularly difficult situation as it creates confusion in the grieving process (Lewis and Bryan, 1988). The parents have the difficulty of mourning one infant while enjoying the survivor. Suppression of the grief response may occur or, in some instances, the surviving twin may be rejected.

Many women will obtain comfort from their minister of religion. Longer term support may be obtained from organizations such as the Stillbirth and Neonatal Death Society (SANDS) which has branches throughout the United Kingdom. It is, however, reassuring for the couple to know that they are welcome to contact a named person at the hospital at any time if they so wish.

Support may be required, not only by the couple, but also by members of hospital staff who may be shocked and distressed by a perinatal death but still have to continue their work and make responsible decisions. Staff need to know how to cope with the stress and whom to approach for help if necessary.

If it becomes evident that a woman is developing a morbid grieving reaction, referral to a psychiatrist or specialist bereavement counsellor will be necessary. Similary, when the baby is abnormal the services of a clinical geneticist may be required.

The principles of management of perinatal death apply equally to miscarriage. Peppers and Knapp (1980) found that there was no quantitative difference in grief responses of women who experienced miscarriage, stillbirth or neonatal death. The emotional needs of women who have experienced a miscarriage have been significantly neglected.

Having recognized the principles of management, it remains for them to be put into practice.

Methods for general implementation include incorporation of specific guidelines into management policies or protocols for antenatal clinics, labour wards, postnatal wards, special care baby units, intensive care units, and community programmes.

Education of midwives and community staff is an important role of the obstetrician. The topic should be included in the curriculum for undergraduate medical education, in introductory lectures for junior doctors beginning their training in obstetrics and gynaecology, in diploma and membership courses in the speciality, and also in revision courses or workshops for trained members of hospital and community staff.

Effective support after perinatal death requires skill, time and continuity of care. These requirements may be difficult to provide in a busy obstetric department. For this reason, the formation of a bereavement team is recommended. As well as providing support in a structured and competent manner, a team approach allows different members to meet different needs of the couple. In my own experience the team comprises a counsellor, a midwife and an obstetrician. A paediatrician may sometimes substitute for the obstetrician.

Immediate medical treatment is provided by the staff on duty at the time of diagnosis of the death or the birth of the infant. The woman is seen by her consultant obstetrician and other members of the bereavement team as soon as possible afterwards. Further visits by members of the team while the woman is in hospital will depend on the circumstances. The contribution of the midwife is of particular value in co-ordinating and maintaining continuity of care while the woman is in hospital as well as after she returns home. It is usual practice for the woman to see her obstetrician again approximately 6 weeks later. The visit should be arranged somewhere other than at the antenatal clinic. A postnatal examination is carried out. The preliminary autopsy report and the results of investigations are explained. Other members of the bereavement team should also be present during part of this visit which constitutes the team's most formal contact with the couple. The timing of the visit is flexible and will be influenced by the needs of the woman as recognized by members of the team. A further visit will be arranged when the final autopsy report is available.

The obstetric and psychological implications for subsequent pregnancies should also be discussed. It is now well established that couples who rush into another pregnancy put themselves at risk of psychological problems (Wolff *et al.* 1970; Forrest *et al.* 1982; Bourne and Lewis 1984); these include inappropriate grief and ambivalent feelings. The woman may have little pleasure in or emotional attachment to the pregnancy and have negative feelings toward the new baby. Couples are advised to wait 6 months to a year before trying for another pregnancy.

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Genetic and familial predisposition to eclampsia and pre-eclampsia in a defined population

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Summary. Familial predisposition and patterns of genetic inheritance of eclampsia and pre-eclampsia were investigated through three or four generations in 94 families from the homogenous island population of Iceland. The families descended from index women delivered in the years 1931-47 and who had either eclampsia (n = 38) or severe pre-eclampsia (n = 69). Inheritance was followed both through sons and daughters. The prevalence of pre-eclampsia and eclampsia in daughters was significantly higher (23%) than that in daughters-in-law (10%). No difference was noted in the prevalence of these diseases by whether the daughter was born of an eclamptic or pre-eclamptic mother or whether she was a first or later born daughter. There was a non-significantly higher occurrence of pre-eclampsia among grand-daughters than in grand-daughters-in-law. No difference was seen by whether grand-daughters descended through sons or daughters. With increasing numbers of affected daughters or grand-daughters the probability rose of finding more affected women in a family. Hypotheses of single recessive and dominant gene inheritance were compared and maximum likelihood estimates for gene frequency obtained. For a single recessive gene model this was 0·31 reflecting a population prevalence of 9·6%, whereas a dominant model with incomplete penetrance gave 0·14 at 48% gene penetrance, corresponding to a population prevalence of 0·9% homozygous expression of severe disease and 11% heterozygous expression of milder disease. Either genetic model could fit the data.

Severe pre-eclampsia and eclampsia have a familial tendency (Humphries 1960; Adams & Finlayson 1961; Chesley *et al.* 1961, 1968) and appear to involve a genetically determined susceptibility possibly based on single gene inheritance (Cooper & Liston 1979; Sutherland *et al.*

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1981; Chesley *et al.* 1986). The pathogenesis of these closely related conditions may be multifactorial, involving coagulation, vascular reactivity or an abnormal immunological reaction between the mother and the fetus (MacGillivray 1983). Some of these abnormalities may be genetically determined. Cooper and Liston (1979) suggested that the inheritance patterns would fit best to a mathematical model consistent with recessive single gene inheritance. It is as yet unclear whether genetic modulation is dependent on the maternal genotype (Sutherland *et al.* 1981; Chesley *et al.* 1986) or on maternal-fetal genetic interaction (Cooper *et al.* 1988, Kilpatrick *et al.* 1989).

Differences in published results may be related to the populations under study. In Iceland there is a homogenous island population with records containing antenatal and delivery information through three or four generations. This population was studied for a possible genetic predisposition to eclampsia and pre-eclampsia. The data were subsequently fitted to genetic models of recessive or dominant single gene inheritance.

Subjects and methods

All 7453 maternity records during the 16 years from 1931 to 1947 at the National University Hospital in Reykjavik were reviewed. Women recorded as having eclampsia or severe pre-eclampsia (index cases) were selected using stringent criteria (Table 1). Those with pre-existing renal or hypertensive disease were excluded.

The national identity files of the Statistical Bureau of Iceland and the computer files of the Genetics Committee of the University of Iceland were consulted to ascertain whether the index woman was alive and to trace her family pedigree. The index woman or her relatives were interviewed. Information was gathered on the size of the family and any possible occurrence of eclampsia, pre-eclampsia or hypertension in the extended family. Criteria in line with those used previously in similar studies (Sutherland *et al.* 1981; Chesley *et al.* 1986) were chosen to classify the descendants (Table 1) and include all relatives at risk. Maternity notes on the women in the study families were obtained from hospitals and maternity homes throughout Iceland and reviewed for evidence of hypertensive disease.

Approval for the study was granted by the National University Hospital ethics committee and the Statistical Bureau of Iceland.

The data were stored on computer in file format and as family trees for each index woman.

χ^2-tests with Yates' correction were used to compare the prevalence of disease between groups. Gene frequency was estimated by the method of maximum likelihood, assuming Mendelian inheritance and random mating. Details of the methods are given with the genetic analysis results.

Results

There were 377 women diagnosed as having hypertension in pregnancy (68% primigravid) but only 156 (63% primigravid) fulfilled the criteria for index cases. Of these 156 women 38 (79% primigravid) had eclampsia and 118 (58% primigravid) had severe pre-eclampsia. Another 49 women fulfilled the criteria for severe pre-eclampsia, but they were excluded from analysis (36 were parous, three had diabetes mellitus and 10 had twin pregnancies).

Eclamptic index women

Thirty of the 38 women had eclampsia in their first pregnancy. Of the eight parous women, two had a previous pre-eclamptic pregnancy and three a normal first pregnancy but for three women, records of the first pregnancy could not be obtained. All except one of the parous women were in their second viable pregnancy. Their mean age was 28 years (range 16–41) and 16 were unmarried. There were three maternal deaths.

Blood pressure measurements were recorded in all but one woman, where it was stated that she had eclampsia and hypertension in pregnancy after she was brought to the hospital with seizures. The mean systolic blood pressure was 178 mmHg (SD 25·0; range 130–240 mmHg) and the mean diastolic pressure was 110 mmHg (SD 16·7; range 80–145 mm Hg). Proteinuria (1 to >3 g/l by the Esbach method) was noted in 30 women. There was no information about proteinuria for three women and five had had negative tests.

There were nine perinatal deaths; nine male and 20 female infants survived. The mean birthweight was 2977 g (range 800–4200 g). Family trees were obtained from 30 women; 17 four generation and 13 three generation families.

Table 1. Definitions for selecting index pregnancies and classifying hypertensive disease in descendants

Index pregnancies:	Eclampsia:	Seizures in hypertensive pregnancy after 20 weeks gestation or within 24 h of delivery
	Severe pre-eclampsia:	BP $\geq$160/110 mmHg with or without proteinuria BP $\geq$160/100 mmHg with proteinuria (After 20 weeks gestation)
Descendants:	Eclampsia:	Seizures in hypertensive pregnancy after 20 weeks gestation or within 24 h of delivery
	Pre-eclampsia:	BP $\geq$140/90 mmHg or rise in systolic $\geq$ 30 or diastolic $\geq$ 15mmHg Presence of proteinuria (After 20 weeecks gestation)

BP = blood pressure.

Pre-eclamptic index women

There were 69 primigravid women with severe pre-eclampsia, of whom 20 were unmarried. Their mean age was 27 years (range 18–40 years). There were two maternal deaths.

The mean systolic blood pressure was 184 mmHg (SD 24·0 range 160–270 mmHg) and the mean diastolic pressure was 116 mmHg (SD 12·5; range 100–150 mmHg). Urinanalysis was available for all but two women. Four had no proteinuria, whereas 17 had $\geq$ 3 g/l on Esbach testing.

There were 14 perinatal deaths; 27 male and 28 female infants survived. Three infants died but no note was made of gender. The mean birthweight was 2928 g (range 1050–4600 g). Family trees of 64 women were obtained of which 27 were four generation and 37 three generation families.

Disease in descendants

The number of daughters and daughters-in-law (second generation descendants) in each disease category are shown in Table 2. Three daughters had eclampsia.

The prevalence of all forms of hypertension (Table 2) in daughters (54 of 120) was significantly different from that seen in daughters-in-law (31 of 104); ($\chi^2_1 = 5{\cdot}5$; $P<0{\cdot}02$). If only descendants with pre-eclampsia are considered, this occurred in 23% (28 of 120) of daughters and in 10% (10 of 104) of daughters-in-law; the difference between the two groups was significant ($\chi^2_1 = 6{\cdot}5$; $P< 0{\cdot}02$). If eclamptic daughters and daughters-in-law were also included the difference in prevalence between the two groups was more significant ($\chi^2_1 = 7{\cdot}5$; $P<0{\cdot}01$).

The prevalence of pre-eclampsia in daughters born of eclamptic mothers (10 of 45; 22%) did not differ significantly from the prevalence in daughters born of pre-eclamptic mothers (18 of 75; 24%). The prevalence of eclampsia or pre-eclampsia was not significantly different between the first born daughters of index mothers and later born daughters.

In Table 3 the prevalence among grand-daughters (16 of 60; 27%) and grand-daughters-in-law (5 of 39; 13%) is shown (third generation descendants). None had eclampsia. The difference in the prevalence of pre-eclampsia was not significant. No difference was seen in the prevalence of pre-eclampsia between grand-daughters by whether they descended through sons (5 of 17; 29%) or daughters (11 of 43; 25%) of the index women.

Grand-daughters with the disease were more often born of affected (5 of 13; 38%) than normal mothers (7 of 34; 21%). In four cases the classification of the mother was not available.

Familial prevalence

Table 4 shows the frequency with which hypertensive disease was found among daughters or grand-daughters by the number of daughters born to the index woman or her direct descendants. In 37% of families at least one daughter with pre-eclampsia was found. With increasing numbers of daughters the probability rose of finding one or more affected daughters. The prevalence rose from 31% in a single daughter family to 67% in three-daughter families. There was no increase in the percentage of the daughters affected. Among grand-daughters not only did the prevalence of affected daughters in the families increase with family size, but also the

Table 2. Numbers of hypertensive and normotensive daughters and daughters-in-law of index women (second generation)

	Index women		
	Eclampsia	Pre-eclampsia	Total
Daughters (total)	45	75	120
Normotensive	24	42	66
All forms of hypertension	21	33	54
Pre-eclampsia	10	18	28
Eclampsia	1	2	3
Daughters-in-law (total)	37	67	104
Normotensive	27	46	73
All forms of hypertension	10	21	31
Pre-eclampsia	3	7	10
Eclampsia	1	0	1

percentage of affected grand-daughters, from 17 to 36%.

Genetic analysis

Hypotheses of single recessive and dominant gene inheritance were tested. The latter fits the data only if incomplete penetrance is assumed. Three groups of women with distinct probabilities for inheriting the disease were available: daughters and grand-daughters of the index cases and daughters-in-law in second and third generations. Under the assumption of random mating, this latter group was used as a random sample of the whole population. The relation of the probability of disease in these three groups to the gene frequency (p) in the population was established using the Hardy-Weinberg principle for equilibrium (Jenkins 1983). These relations were used to obtain maximum likelihood estimates of the gene frequency. For dominant inheritance, penetrance was estimated simultaneously.

The gene frequency was estimated for a single gene recessive model (Table 5) to be 0·31 with a 95% confidence interval of 0·26 to 0·37. By the Hardy-Weinberg equation p^2 reflects a prevalence of 9·6% of pre-eclampsia in the population.

In Table 6 the observed and expected numbers of affected and not affected relatives of the index women are shown for a model of dominant inheritance with incomplete penetrance. χ^2 values based on the likelihood ratios were calculated for a grid of values (Table 7). The lowest χ^2 value indicates the maximum likelihood, that

Table 3. Numbers of hypertensive and normotensive grand-daughters and grand-daughters-in-law of index women (third generation)

	Index women		
	Eclampsia	Pre-eclampsia	Total
Grand-daughters (total)	23	37	60
Normotensive	12	21	33
All forms of hypertension	11	16	27
Pre-eclampsia	7	9	16
Eclampsia	0	0	0
Grand-daughters-in- law (total)	10	29	39
Normotensive	6	22	28
All forms of hypertension	4	7	11
Pre-eclampsia	2	3	5
Eclampsia	0	0	0

Table 4. Familial prevalence of pre-eclampsia and eclampsia in pregnancies of daughters of index cases

Daughters in family (*n*)	Families (*n*)	Daughters (*n*)	Pre-eclampsia Cases (*n*)	Families (%)	Daughters (%)
1	42	42	13	31	31
2	14	28	6	43	21
3	9	27	7	67	26
≥4	7	23	5	57	22
Total	72	120	31	37	26
Grand-daughters in family (*n*)		Grand-daughters (*n*)			
1	18	18	3	17	17
2	10	20	5	50	25
≥3	8	22	8	75	36
Totals	36	60	16	39	27

most likely to be nearest to the true value. The maximum is hence at a gene frequency of 0·14 and 48% penetrance (b) The χ^2 value for the goodness of fit was 2·02 (1 df). As the two indices were allowed to move away from the maximum, the χ^2 values increased and the 95% confidence limit is reached when χ^2 has increased by the critical value for 2 df (5·99) to 8·01

In dominant inheritance (Table 6) the proportion of individuals homozygous for the gene and expressing it ($p^2\times b$) would be 0·9%. These would be expected to develop a severe form of the disease. The proportion of heterozygous individuals expressing the gene ($2(p-p^2)\times b$) would be 11% and these would have a milder form of the disease.

Discussion

For studying the possible genetic contribution towards hypertensive disease in pregnancy this population has several advantages. It is uniformly Caucasian-Nordic and has until this century lived in relative isolation. Records of antenatal care and delivery have been kept since 1931. A national registry, ready access to stored data on population genetics and a strong interest in genealogy in the country proved helpful in tracing family pedigrees. It was possible to verify verbal information by access to case records. In contrast to previous studies we were able to trace third and fourth generation descendants not only through daughters but also through sons.

The index women (probands) were selected by using strict criteria for both eclampsia and severe pre-eclamptic disease. It may be argued that these are two separate diseases, but in general they are regarded as closely related, and this is supported by clinical and pathological evidence linking these two conditions (Robertson *et al* 1967, MacGillivray 1983). As in the study of Chesley and Cooper (1986) the criteria for probands were stricter than those used in descendants to maximize the chance that they really had the specific hypertensive disease of pregnancy We included a few parous women with eclampsia among the probands since their condition was as carefully recorded as that of the primiparous eclamptic women. The proportion of parous women among our index cases was 7·5%, which appears lower than in the series studied by Chesley *et al.* (1968). In our study the prevalence of pre-eclampsia among daughters was the same regardless of whether the mother had eclampsia or pre-eclampsia and was higher than in the control group of daughters-in-law. Moreover, two of the women with pre-eclampsia had daughters with eclampsia while one pre-eclamptic daughter was born of an eclamptic mother. By the third generation, eclampsia was no longer seen which may reflect changing maternity care.

In previous studies the simplest hypothesis, single recessive gene inheritance, has been tested (Cooper & Liston 1979, Sutherland *et al.* 1981, Chesley & Cooper 1986, Cooper *et al* 1988) and has been supported by data on HLA-DR4 sharing (Kilpatrick *et al.* 1989). Our aim was to test our data by the same method and to

Table 5. Test of single recessive gene hypothesis Observed and expected (in brackets) numbers of affected and not affected individuals in various classes of relatives

		Daughters	Daughters-in-law	Grand-daughters	Grand-daughters-in-law	p	χ^2
Expected proportion	Normal	$1-p$	$1-p^2$	$1-\frac{1}{2}p(1+p)$	$1-p^2$		
	Affected	p	p^2	$\frac{1}{2}p(1+p)$	p^2		
	Normal	89(83)	93(94)	44(48)	34(35)	0·31	3·32
	Affected	31(37)	11(10)	16(12)	5(4)		(2 df)

All women with hypertension and proteinuria considered affected.
95% confidence interval 0·26 to 0·37.
$\chi^2 = -2 \times$ natural logarithm of maximum likelihood estimate.

attempt a more complicated analysis, to assess the possibility of dominant inheritance with incomplete penetrance. The existence of incomplete penetrance of a dominant gene is known in other conditions such as ovarian cancer (Heintz *et al.* 1985) and its occurrence in pre-eclampsia may be supported by the development of pre-eclampsia in only 50% of women with risk factors (Wallenburg *et al.* 1986) This hypothesis would explain different degrees of severity of the syndrome through hetero- and homozygosity.

In the genetic analysis of hypertensive disease in pregnancy additional problems are encountered because the condition is expressed in women only in the latter half of pregnancy and exhibits varying degrees of severity. To what extent maternal-fetal genome interaction is responsible for the disease is unknown, and this further complicates analysis.

Our data confirm the previous observations of a strong familial susceptibility to eclampsia and pre-eclampsia (Humphries 1960; Adams & Finlayson 1961; Chesley *et al.* 1968, Cooper & Liston 1979; Sutherland *et al* 1981; Chesley & Cooper 1986, Cooper *et al.* 1988, Kilpatrick *et al* 1989). The studies of Cooper and Liston (1979) suggested that inheritance patterns would fit best to a model consistent with recessive gene inheritance, but it was not possible to show whether this was wholly dependent on maternal or fetal genetic influences. Sutherland *et al* (1981) showed conclusively that fetal genetic influences alone could not be operative and our findings support this, since if the fetal genotype was alone responsible for the inheritance, the prevalence amongst daughters and daughters-in-law would be the same. Subsequent studies have supported a maternal influence (Chesley *et al.* 1986), while others have suggested some contribution by the fetal genotype (Cooper *et al* 1988, Kilpatrick *et al.* 1989). If, however, the maternal genotype were wholly determining, then differing grades of severity of disease would be dependent on degree of penetration (or expression) of the gene.

The interesting finding in this study is that the

Table 6. Test of single dominant gene hypothesis. Observed and expected (in brackets) numbers of affected and not affected individuals in various classes of relatives

	Daughters	Daughters-in-law	Grand-daughters	Grand-daughters-in-law	p	b	χ^2
Normal	89(85)	93(91)	44(48)	34(34)	0·14	0·48	2·02
Affected*	31(35)	11(13)	16(12)	5(5)			(1df)

*All women with hypertension and proteinuria considered affected
Expected proportion· Affected daughters: $(1-(1-p)^2/(2-p))\times b$.
Affected daughters in law. $(1-(1-p)^2)\times b$
Affected grand-daughters. $(1-(1/2((1-p)^2/(2-p)+(1-p)^2))\times b$
b=penetrance of the gene p=frequency of the gene.
$\chi^2 = -2 \times$ natural logarithm of the likelihood ratio

Table 7. Calculation of χ^2 values from the likelihood function, showing the relation between penetrance (b%) and gene frequency (p%) in dominant inheritance for daughters, grand-daughters and daughters-in-law (combined second and third generation).

Frequency of the gene	Penetrance of the gene (%)				
	40	44	48	52	56
0·20	2·78	3·62	5·86	9·36	14·03
0·17	2·54	2·24	3·28	5·54	8·89
0·14	3·58	2·15	2·02	3·05	5·17
0·11	6·46	3·90	2·61	2·45	3·28
0·08	12·23	8·57	6·15	4·80	4·40

Women with pregnancy induced hypertension and proteinuria considered affected. The 95% confidence limit for the indices is $\chi^2 = 8{\cdot}01$.

condition fits both genetic models quite closely. The gene frequency in the population studied was estimated to be around 0·31 for the single gene recessive model, reflecting a calculated prevalence of 9·6% (95% confidence interval 6·8–13·7%) for pre-eclampsia and eclampsia. Although penetrance was not estimated for the model with recessive inheritance, it is clear that a model with appreciable deviation from full penetrance would also fit the data, and then the estimated frequency of the gene in the population would be higher.

Development of eclampsia or pre-eclampsia may be based on dominant inheritance with incomplete penetrance. The penetrance might then theoretically be dependent on the fetal genotype. Whether descent was through a son or daughter of the index woman did not appear to matter, but affected grand-daughters were nearly twice as often the offspring of an affected mother than of a normal mother. If the disease is dominantly inherited, with incomplete penetrance, an affected daughter of the index pregnancy is an obligate carrier of the gene, whereas a normal daughter or a son would have a 44% or 60% chance respectively, of possessing the gene. This would explain the higher prevalence of the condition in the grand-daughters who were offsprings of an affected mother. Multifactorial inheritance has not been excluded.

Hypertensive complications of pregnancy are common and demand considerable health service resources. There are no reliable methods for predicting which women may develop gestational hypertensive disease. If a group of women at increased risk were defined, it would be possible to concentrate resources on these patients. Pedigree analysis could be of use in this respect, but for counselling to be possible on the basis of family history, there must be more knowledge of inheritance patterns. Molecular genetic methods will, however, be required to provide information on the exact mode of inheritance in eclampsia and pre-eclampsia.

Acknowledgments

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Pelvic floor damage and childbirth: a neurophysiological study

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Summary. Ninety six nulliparous women were investigated to establish whether childbirth causes damage to the striated muscles and nerve supply of the pelvic floor. The techniques used were concentric needle electromyography (EMG), pudendal nerve conduction tests and assessment of pelvic floor contraction using a perineometer. There was EMG evidence of re-innervation in the pelvic floor muscles after vaginal delivery in 80% of those studied. Women who had a long active second stage of labour and heavier babies showed the most EMG evidence of nerve damage. Forceps delivery and perineal tears did not affect the degree of nerve damage seen. We conclude that vaginal delivery causes partial denervation of the pelvic floor (with consequent re-innervation) in most women having their first baby. In a few this is severe and is associated with urinary and faecal incontinence. For some it is likely to be the first step along a path leading to prolapse and/or stress incontinence.

Traditionally obstetric trauma has been implicated in the development of genital tract prolapse, genuine stress incontinence and anorectal incontinence. Smith *et al.* (1989a, 1989b) and Gilpin *et al.* (1989) have used single fibre electromyography (EMG), pudendal nerve conduction tests and muscle histochemistry to show that women with stress incontinence of urine and/or genital tract prolapse have evidence of partial denervation of the pelvic floor muscles. Neill and Swash (1980) have shown that faecal incontinence is associated with re-innervation of the external sphincter muscle. Snooks *et al.* (1984) showed that primiparous and multiparous women who did not have a caesarean section had increased re-innervation of the external anal sphincter 2 months after delivery and that multiparous women who had forceps delivery had increased pudendal nerve terminal motor latency to the anal sphincter 2 months after delivery.

The aim of this study was to establish whether the muscles and nerve supply of the pelvic floor undergo such changes as a result of childbirth.

Subjects and methods

The women studied were recruited from hospital antenatal clinics. Primigravid women were selected because multiparous women with no prolapse and normal urinary control are known to have pelvic floor denervation in comparison with nulliparous women of the same age (Smith *et al.* 1989a).

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The techniques used were concentric needle EMG, pudendal nerve terminal motor latency measurements and an assessment of the power of the pelvic floor muscle by measurement of intravaginal pressure.

Recruitment was at 36 weeks gestation A detailed history was obtained recording details of urinary symptoms before and during pregnancy), medical history, family history, employment and exercise history. All the women had a general physical and obstetric examination, and during the vaginal examination the woman was asked to contract her pelvic floor muscles (this was done to see that she was able to contract the correct muscle group, namely, the pelvic floor, on request). An assessment of the power of the pelvic floor muscles was made during three consecutive contractions using a digital perineometer. A concentric needle EMG of the pelvic floor was then recorded. The left side was chosen to avoid recording iatrogenic damage to the muscle after right medio-lateral episiotomy Previous work has shown no difference between EMG recordings on the right and left sides of the pelvic floor (Smith, 1985).

A detailed record was kept of the events occurring in labour and during delivery in women in the study. Before discharge, between 2 and 5 days after delivery, pudendal nerve conduction was measured and the pelvic floor power was assessed by perineometry. Women were seen again 2 months after delivery when a detailed questionnaire was completed recording details of exercise and changes in urinary control. The three tests, pelvic floor contraction, concentric needle EMG and pudendal nerve conduction, were all repeated.

Of the 96 women attending for antenatal tests 82 tolerated the needle insertion and movement required for concentric needle EMG. Of the 78 women who returned for the postnatal test at 2 months, 75 were willing for the concentric needle EMG to be repeated.

Measurement of pelvic floor contraction

Damage to the muscle innervation may result in loss of muscle power. Assessment of the power of the pelvic floor muscles during a voluntary contraction was made using a perineometer The device (Fig. 1) is based on a design used by Kegel (1951). Pressure changes in the vagina are detected by the cuffed catheter, transmitted to a piezo-resistive pressure transducer and values displayed Three measurements of the power of the pelvic floor were made at each of the three visits.

Concentric needle electromyography

Concentric needle EMG was chosen in preference to single fibre EMG to enable assessment of 'interference patterns' and to allow individual motor unit analysis before and after delivery.

Interference pattern. This was observed at rest and during voluntary activity. At rest single motor unit potentials in the range of the needle electrode are visible on the oscilloscope screen of the Medelec MS6 electromyography machine. During contraction of the pelvic floor muscle additional motor units are recruited and appear on the screen. At the height of the contraction individual motor unit potentials superimpose, giving a dense pattern of electrical activity in which individual motor unit electrical discharges are no longer visible. This is defined as a full interference pattern When the nerve supply to a muscle is damaged or diseased it is no longer possible to recruit the maximum number of motor units during a voluntary contraction. This affects the interference pattern, which may become reduced or lost altogether.

Motor unit analysis. Analysis of individual motor units in pelvic floor muscles allows assessment of the EMG changes associated with partial denervation and consequent re-innervation These consist of alterations in the configuration, duration and amplitude of the motor unit potential (MUP) and are illustrated in Figs. 2 and 3. Loss of synchronization of muscle fibre discharge with slow conduction in nerve terminals or muscle fibres, dispersion of end plate location or longer nerve terminals causes polyphasic potentials (Daube 1981) These are potentials which have five or more phases (a phase being that part of the signal between two zero crossings). Polyphasic potentials usually make up less than 10% of MUPs and as a non specific finding are increased in a number of disorders of nerve and muscle. The duration of a MUP is increased when denervated muscle fibres are re-innervated by sprouts from adjacent healthy nerve twigs. For this reason duration of the MUP is probably the most valuable factor to assess damage to pelvic floor innervation The MUP amplitude also increases as re-innervated motor units become more compact, but it is to some extent dependent on the distance between

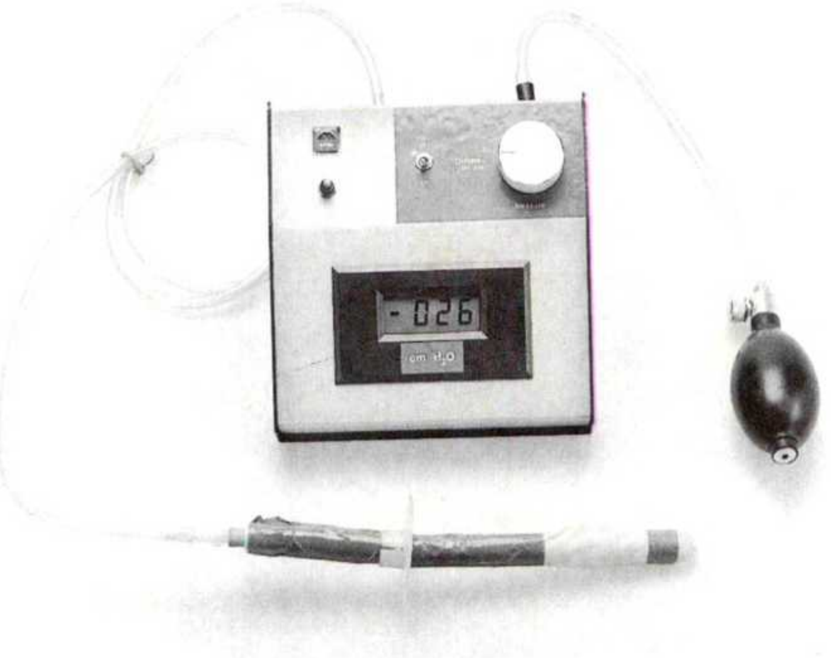

Fig. 1. The digital perineometer.

the recording electrode and the active muscle fibres.

Technique. EMG activity of the left side of the pelvic floor was recorded using a 75 × 0·65mm concentric needle electrode connected to a Medelec MS6 electromyographic recording system. A ground electrode attached to the patient's right thigh reduced electrical interference. The muscle belly of pubococcygeus was palpated with the examining right hand in the vagina and the needle electrode was then guided into position. The length of the needle made it possible for further positional adjustments to be made from outside the vagina. The signals picked up from the muscle by the electrode were displayed on the oscilloscope screen accompanied by an audio output. Operation of a foot-switch allowed recordings to be transferred to Kodak light sensitive paper as a permanent copy. With the needle electrode in position, the EMG activity at rest was recorded with a sweep speed of 100 ms/division. The patient was then asked to contract her pelvic floor and a recording was made during the muscle activity. This demonstrated the recruitment of muscle fibres within the range of the recording electrode giving the interference pattern.

The sweep speed was then reduced to 2 ms/division and individual motor units were isolated with the patient at rest using an SDS6 signal delay module incorporated in the MS6 machine. This device enabled the display to be triggered from the largest action potential in the electrode range whilst preserving pretrigger events. The position of the needle was adjusted in the muscle to obtain up to 20 individual motor units. These

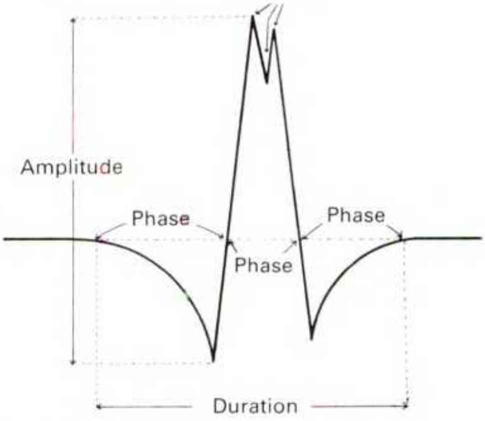

Fig. 2. Schematic diagram of the characteristics of a motor unit potential.

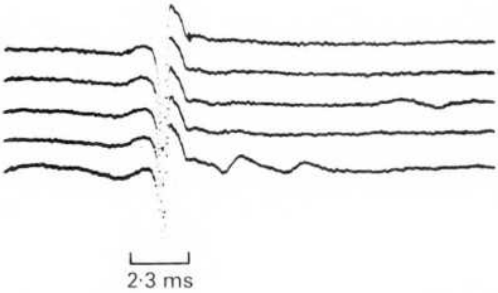

Fig 3a. Five consecutive recordings from the same motor unit typical of normally innervated muscle, i.e. relatively short duration and less than five phases.

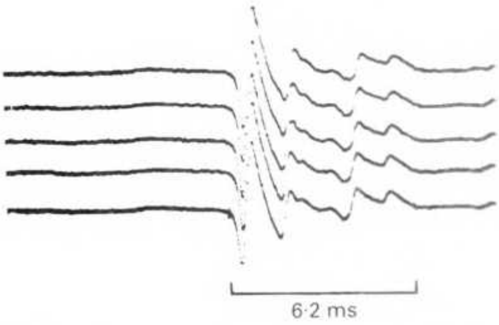

Fig 3b. Five consecutive recordings from the same motor unit displaying features associated with re-innervation as a consequence of partial denervation, i.e. relatively long duration and polyphasia.

motor units were analysed at a later date; to record the duration and amplitude of the motor unit and whether or not it was polyphasic.

Pudendal nerve conduction tests

Pudendal nerve stimulation tests were performed between 2 and 5 days after delivery and again 2 months later. Changes in conduction time reflect the integrity of large myelinated fibres in the pudendal nerve. Prolonged conduction times suggest nerve damage. Pudendal nerve stimulation was performed in the left lateral position. A Disa 21L10 platinum ring electrode mounted on a size 10 (French) Foley catheter was introduced into the urethra. The electrode used to record the response of the pubococcygeus muscle was constructed from a 9 mm cuffed endotracheal tube with two 4 × 10 mm brass surface electrodes fixed either side of the cuff. The tube was inserted into the vagina and the cuff inflated with air so that the surface electrodes came to rest against the pubococcygeus muscle. The pudendal nerve stimulator was modified from the gloved rectal device used by Smith (1985b) and described by Kiff and Swash (1984). It was slimmer and caused less discomfort on insertion. The device was made from a 9 mm endotracheal tube with the cuff removed (Fig. 4), the end of the tube was sealed and two stimulating electrodes were fixed at the tip. Two brass surface electrodes were fixed 4·5 cm from

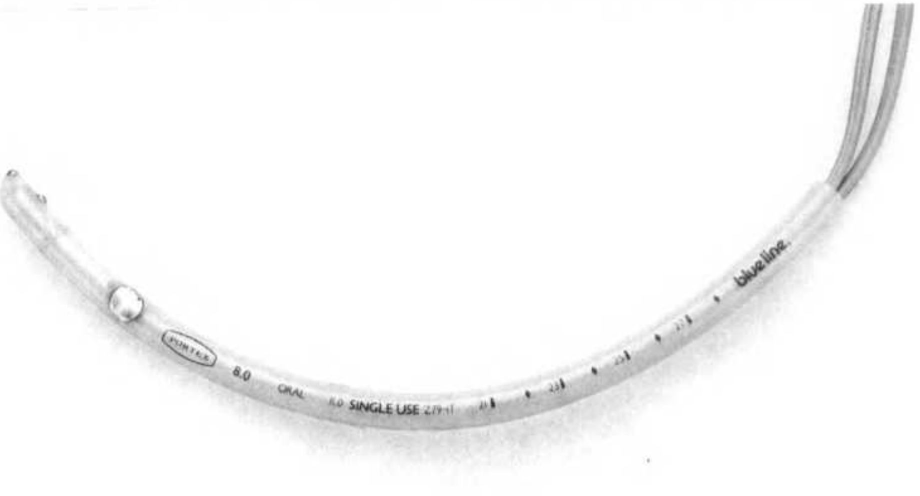

Fig. 4. Intra-rectal pudendal nerve stimulator.

Table 1. Motor unit potential characteristics before and after delivery

Motor unit potential	Antenatal ($n = 82$)	Postnatal ($n = 75$)	*P*
Mean duration (ms)	3·3 (0·6)	5·2 (1 5)	<0·00001
Mean amplitude (μV)	498 (189)	566 (290)	0·639
Frequency of polyphasia (%)	9·6 (11·9)	36·3 (18·0)	<0·00001

Results are mean (SD) values

the tip of the stimulator. A malleable central wire stiffened it sufficiently so that the stimulating tip could be directed towards the pudendal nerve on either side as it crossed the ischial spine.

With all the electrodes in place a pulsed stimulus of 0·1 ms duration and 25–150 V was given every second to the pudendal nerve via the intrarectal stimulating electrode. The position of the electrode was adjusted until a minimum conduction time with maximum amplitude of response was obtained

The stimulus-to-response time was measured when a supramaximal stimulus was given Responses were recorded for the anal sphincter, pubococcygeus and urethral sphincter on both right and left sides.

Results

Pelvic floor contraction

The change in vaginal pressure generated by a pelvic floor contraction was measured on three occasions in 50 women.

The maximum contraction pressure measured at each visit was used to derive a mean for the group. The mean maximum contraction pressure was 15·6 (SD 9·2) cm H_2O at the antenatal visit, 5·4 (SD 4·9) cm H_2O at 2–5 days after delivery and 10·1 (SD 6·9) cm H_2O at 2 months after delivery. There was wide variation in the power of the pelvic floor between women. However, in most, delivery substantially reduced the power of the pelvic floor to contract. Using Wilcoxon's matched pairs signed rank test, there was a significant reduction immediately after delivery (P=0·00002) with some recovery at 2 months postnatal (P=0·00032) but not to the original antenatal power (P=0·00056).

Concentric needle EMG

Interference pattern. Antenatally the interference pattern was full in all the women. At the 2 months postnatal visit four women showed a reduced interference pattern One complained of stress incontinence before pregnancy and all four had stress incontinence 8 weeks after delivery.

Individual motor unit analysis. For each woman, at both the antenatal and postnatal visits, a mean duration and amplitude was calculated from the recorded MUPs. In addition, the proportion of polyphasic potentials for each woman at both visits was expressed as a percentage of the total number of motor units analysed per woman. The results have been examined in two ways. The mean duration, amplitude and proportion of polyphasic potentials in the 82 women assessed before delivery were compared with the EMG findings in the 75 women assessed after delivery. These findings which are illustrated in Table 1 and Figures 5, 6 and 7 show a significant increase in the duration of MUPs and in the proportion of polyphasic potentials postnatally. There was no significant difference in MUP amplitude between these two groups (Mann-Whitney *U* test). These findings demonstrate that delivery causes damage to the innervation of pelvic floor muscles The second way of expressing the findings is by a histogram to show how this damage is distributed among the women studied (Fig 8). In it motor duration (i.e., the most sensitive indication of nerve damage) has been compared in individual women before and after delivery. The distribution of this indicator of nerve damage is wide. Of the 66 women who had complete EMG measurements at both the antenatal and postnatal investigations, 13 showed either no change or one within the error of the investigation. In five women there was a prolongation of MUP >120% of the antenatal value. It is noteworthy that all five women were incontinent of urine at 8 weeks after delivery compared with 21 (34%) in the rest of the group. This difference is statistically significant (P=0·01472, Fisher's exact test).

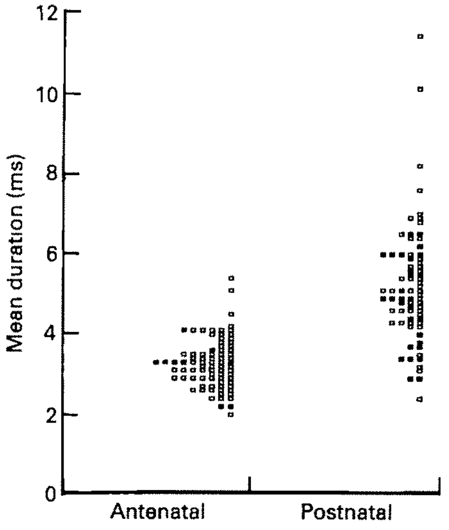

Fig. 5. Mean motor unit potential durations at 36 weeks gestation and 8 weeks postnatal. Each square represent the mean duration in one patient (corrected to the nearest 0·1 ms)

There was no significant difference (P=0·838) in the mean MUP duration between the 34 women who had a normal vaginal delivery (5·5, SD 1·2 ms) and the 24 women who had a forceps delivery (5·5 ms—S.D. 2.0 ms).

The three women (Table 2) who were delivered by an elective caesarean section before labour had MUP durations after delivery which were comparable to their antenatal values (paired t-test), suggesting that their pelvic floor had been spared denervation damage. Women who had a caesarean section during labour had increased MUP duration compared with their antenatal values. This finding implies that labour itself is important in the denervation damage sustained during childbirth.

Apart from labour and vaginal delivery, the other factors which influence the degree of denervation of the pelvic floor, as demonstrated by increased MUP duration and polyphasia, are the length of the second stage of labour and the weight of the baby. The mean duration of the second stage of labour in the women who were delivered vaginally was 83·2 min. This comprised a mean passive phase of 29·7 min and a mean active phase of 56.7 min. Table 3 shows that there was a significant increase in the postnatal MUP duration in women who had a longer than average total second stage of labour This increase in MUP duration was confined to those whose active second stage was above average in duration.

The mean weight of the babies born to the study women was 3·41 kg. There was a small but significant increase in the MUP duration postnatally in the women who had heavier than average babies (Table 4). This was not due to an increased second stage labour, for the length of the second stage in these women was not significantly different from that in women who had a baby of below average weight.

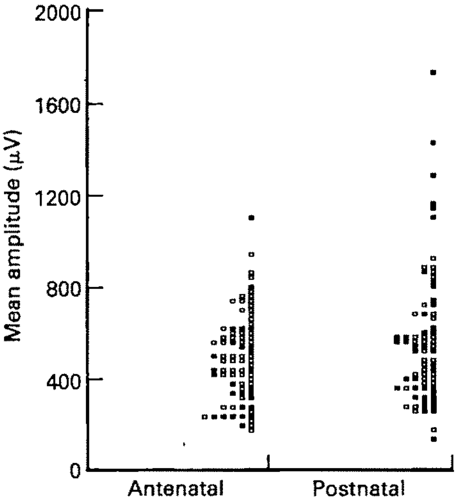

Fig. 6. Mean motor unit potential amplitudes at 36 weeks gestation and 8 weeks post-natal. Each square represents the mean amplitude in one patient (corrected to the nearest 20 μV)

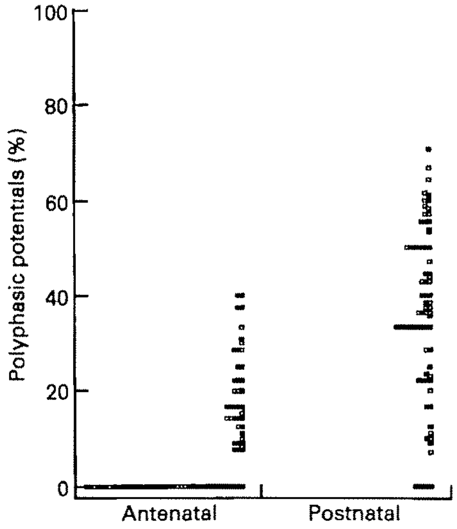

Fig. 7. The incidence of polyphasic potentials at 36 weeks gestation and 8 weeks postnatal. Each square represents the incidence in one patient.

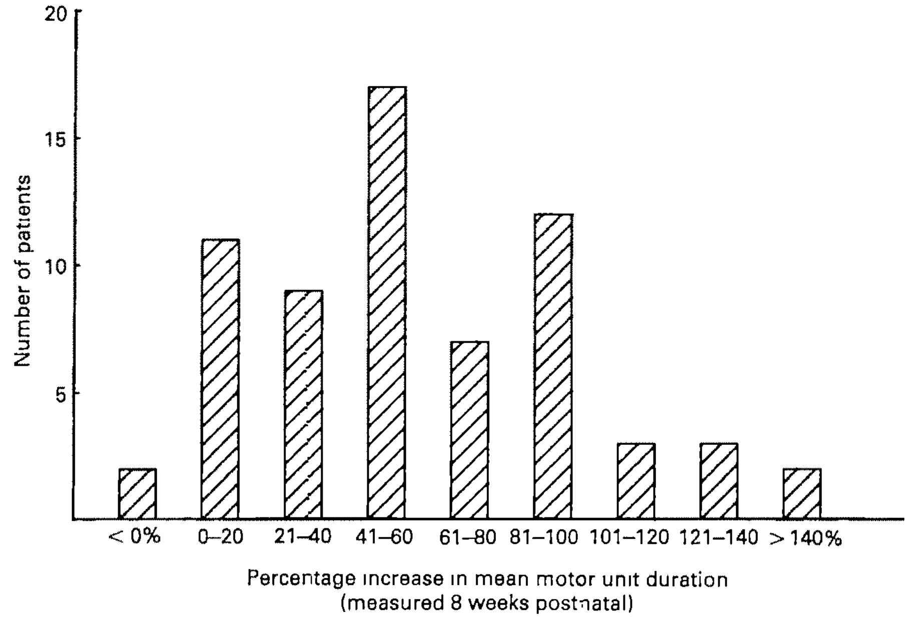

Fig. 8. Histogram showing individual changes in motor unit potential duration at 8 weeks postnatal compared with antenatal values.

If the factors of a longer second stage and a heavier than average baby are combined and compared with the factors of a shorter second stage and a smaller than average baby, there is a significant difference in the MUP duration between the two groups (Table 4). This suggests that the former group sustain more pelvic floor damage and show more evidence of reinnervation postnatally. In this group, 55% had stress incontinence of urine at 8 weeks after delivery compared with 20% in the group who had a relatively short second stage of labour and a smaller than average baby. This difference is statistically significant (P=0·032; χ^2).

The following factors were examined and found not to influence the degree of pelvic floor damage in terms of increasing the postnatal mean MUP duration. (1) Patient characteristics, (age, height, weight, body mass index); (2) length of the first stage of labour; (3) length of the passive phase of the second stage of labour; (4) whether labour was spontaneous or induced; (5) intravenous oxytocic drugs; (6) epidural analgesia; (7) forceps delivery; (8) episiotomy or tears; (9) occipito-frontal head circumference of the baby; and (10) pelvic floor exercise (antenatal/postnatal)

Pudendal nerve conduction tests

Pudendal nerve conduction tests were performed between 2 and 5 days after delivery (post-partum) and again 2 months after delivery (postnatal) The conduction times (latencies) of the pudendal nerve to the anal sphincter, pubococcygeus muscle and urethral sphincter were measured. For each woman a mean time was calculated from the value obtained on the right and

Table 2. Motor unit potential durations before and after delivery by caesarean section

	Duration of motor unit potentials (ms)		
Caesarean section	Antenatal	Postnatal	*P*
Elective (n = 3)	3·2 (0·7)	3.4 (0·9)	0·535
Emergency (n = 5)	3 6 (0 6)	5.1 (0·6)	0·008

Results are mean (SD) values

Table 3. Effect of the length of the second stage of labour on postnatal motor unit potential (MUP)

Second stage	*n*	MUP duration (ms) mean (SD)	*P*
Total length			
≤83·2 min	37	4·8 (1·2)	
>83·2 min	35	5·7 (1·6)	0·004
Passive phase			
≤29·7 min	48	5·4 (1·6)	
>29·7 min	21	5·0 (1·2)	0·771
Active phase			
≤56·7 min	34	4·9 (1·4)	
>56·7 min	36	5·6 (1·6)	0·025

left sides. Previous work has shown that there is no difference between the two sides (Smith, 1985).

Table 5 shows that there was no significant difference in the mean pudendal nerve conduction times between the immediate post-partum and the 2 month postnatal measurements.

Discussion

This study shows that the power of the pelvic floor to contract is impaired by vaginal delivery and at 2 months has not regained the power seen in pregnancy. The EMG changes of increase in the MUP duration and polyphasia show that vaginal delivery causes partial denervation of the pelvic floor in 80% of women delivering their first baby. For a few this damage was severe and associated with loss of urinary control.

There was no increase in mean motor unit amplitude postnatally. However, any increase in amplitude due to motor units compacting and being re-innervated by a shared nerve supply may well take longer than the 2-month interval in this study. The 2-month interval was chosen because it is believed that most re-innervation as a consequence of significant nerve damage would have taken place by then and because of the convenience of coinciding EMG studies with the traditional timing of the postnatal visit.

The pudendal nerve conduction tests showed no significant differences between the results seen in the immediate puerperium compared with the results obtained 2 months postnatally. We would have liked to compare these conduction times with antenatal values. However, it was considered unethical to stimulate the pudendal nerve of pregnant women. Snooks *et al.* (1984), in a postnatal study, found pudendal nerve conduction times at 2-3 days post delivery to be marginally increased when compared with non-pregnant healthy multiparous women. By 2 months post-partum, recovery had occurred and they could find no difference

Table 4. Effect of birthweight alone and in combination with length of second stage on postnatal motor unit potential (MUP) duration

	n	MUP duration (ms) mean (SD)	*P*
Birthweight kg			
≤3·41	38	4·8 (1·1)	
>3·41	37	5·6 (1·7)	0·023
Second stage and birthweight			
≤83·2 min			
≤3·41 kg	22	4·4 (0·9)	
>83·2 min			
>3·41 kg	20	5·9 (1·8)	0·0008

Table 5. Pudendal nerve conduction times (latencies) at the post-partum and postnatal examinations

	Latency (ms)				
	Postpartum		Postnatal		
	n	mean (SD)	*n*	mean (SD)	*P*
External anal sphincter	55	1·9 (0 2)	58	1·9 (0·2)	0·529
Pubococcygeus	49	2 0 (0 3)	55	2 0 (0·2)	0·941
Urethral sphincter	23	2 1 (0 2)	45	2·1 (0·3)	0·591

between primipara and multipara delivered normally and their control group. However, multipara delivered by forceps still had prolongation of nerve conduction times at this stage. Pudendal nerve terminal motor latency measurements are useful in detecting gross damage to the pelvic floor innervation such as found in patients with anorectal incontinence (Snooks *et al.* 1985), genital tract prolapse or stress incontinence of urine. To obtain prolonged pudendal nerve conduction times there needs to be significant loss or damage to the large myelinated, fast conducting fibres in the pudendal nerve (Kiff & Swash 1984; Smith 1985). It seems that any damage to the pudendal nerve caused by the first vaginal delivery is too small to be detected by conduction time tests.

The most significant finding of this study is that vaginal delivery causes partial denervation of the pelvic floor in most women. It seems that a minority of women give birth with very little evidence of nerve damage to the pelvic floor while most experience some damage and a few show evidence of severe denervation which is associated with loss of urinary control. Events such as forceps delivery and perineal tears do not significantly affect innervation We were surprised by the lack of correlation between denervation damage and most of the traditional factors thought to play a part in causing prolapse The finding that uncomplicated labour and delivery causes denervation in most women is gloomy news to an obstetric attendant trying to minimize damage. It seems that certain women are constitutionally at risk from nerve damage to their pelvic floor as a result of the birth of their first baby. The only significant factor we have identified that can be influenced by management is a long active second stage. The traditional philosophy of not pushing until the head is visible and the shortening of a long active second stage by an episiotomy or even forceps has merit in as much as these practices minimise the risk of denervation damage of the pelvic floor.

It is unclear whether the EMG changes seen were due to stretching of the pudendal nerve or to a direct pressure effect of the fetal head on small branches of the nerve or at the myoneural junction. A major issue is the relevance of the denervation seen as a result of the first delivery to the aetiology of genital prolapse, urinary stress incontinence and faecal incontinence For most women the degree of denervation was slight. However, in a few the damage was severe and symptomatic. Denervation progresses with ageing and it is likely that further denervation will occur with future deliveries. We suspect that, for some women, the first delivery is the first event on a path leading to prolapse and stress incontinence. We plan to follow this group of women over the years to measure the innervation of the pelvic floor and relate any changes observed to urinary and faecal control and the occurrence of genital tract prolapse.

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Epidemiology of pelvic inflammatory disease in parous women with special reference to intrauterine device use

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Summary. Up to the end of 1989, 206 parous women in the Oxford Family Planning Association contraceptive study had been referred to hospital with a first episode of pelvic inflammatory disease. Of these, 65 suffered from definite disease described as acute, 81 from definite disease not described as acute and 60 from 'other disease'. Considering all forms of disease together, referral was less common in those aged 25–29 and in those aged 45 or more than in those aged 30–44. Referral was more common in those of low social class, in those who smoked and in those who married young. All these factors were taken into account in analyses considering the effects of contraceptive methods. In these analyses, women currently using the contraceptive pill, the diaphragm, the sheath, female sterilization or an intrauterine device (IUCD) were compared with those currently using other methods or no method of contraception. IUCD ex-users were, however, placed in a separate category, irrespective of their current method of contraception. The relative risks obtained in these analyses, with 95% CI, were as follows: contraceptive pill 0·5 (0·2–0·9), diaphragm 0·6 (0·3–1·2), sheath 1·2 (0·6–2·4), female sterilization 0·7 (0·3–1·5), non-medicated IUCD 3·3 (2·3–5·0), medicated IUCD 1·8 (0·8–4·0), IUCD ex-users 1·3 (0·7–2·3). These data suggest that oral contraceptives, the diaphragm and female sterilization protect against pelvic inflammatory disease and that IUCDs increase the risk. Medicated devices, however, appear to carry only about half the risk of non-medicated devices, and the elevation of risk in IUCD ex-users appears to be small. Special analyses examined the risk associated with use of a Dalkon Shield. Among women currently using an IUCD (of any kind), those who had used a Dalkon Shield (at any time) had nearly five times as great a risk of hospital referral for pelvic inflammatory disease as those who had never used a Dalkon Shield (relative risk 4·7, 95% CI 2·1–9·0).

In 1981, we reported on the occurrence of pelvic inflammatory disease among parous women taking part in the Oxford Family Planning Association contraceptive study (Vessey *et al.* 1981). We found that the risk of hospital admission for 'acute definite' disease among

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women using an intrauterine contraceptive device (IUCD) was 10·5 times higher (95% CI 5·4 to 32) than that among women using other methods or no method of birth control. There was little evidence of any increased risk of such disease in ex-users of an IUCD. Hospital admission for 'chronic definite' disease, on the other hand, was commoner in ex-users of an IUCD than in current users.

While these findings fitted in well with the results of other studies available at that time, a World Health Organization Scientific Group (1987) has suggested that the risks of acute pelvic inflammatory disease associated with IUCD use have been overestimated. In particular, it has been pointed out that the clinical diagnosis of pelvic inflammatory disease is unreliable and may be biased by knowledge of contraceptive method, that users of occlusive methods of contraception and of oral contraceptives do not provide a satisfactory comparison group because these birth control methods protect against pelvic inflammatory disease, that sexual behaviour is important in the aetiology of pelvic inflammatory disease but has been ignored as a confounding variable in most studies, and that much of the excess risk is associated with older non-medicated IUCDs (especially the Dalkon Shield) rather than with more modern medicated devices.

These considerations encouraged us to take a further look at the epidemiology of pelvic inflammatory disease in the Oxford Family Planning Association study and we report our findings here up to the end of 1989.

Subjects and methods

A detailed description of the methods used in the study has been given elsewhere (Vessey *et al.* 1976). In brief, 17 032 women were recruited at 17 large family planning clinics in England and Scotland between 1968 and 1974 inclusive. At the time of recruitment, each woman had to be: (a) aged 25–39 years, (b) married, (c) white and British, (d) willing to participate and (e) either a current user of oral contraceptives of at least 5 months' standing or a current user of a diaphragm or an IUCD of at least 5 months' standing without previous exposure to the pill. During follow-up, each subject is questioned by a doctor or a nurse at return visits to the clinic and certain items of information are noted on a special form. These include details of pregnancies and their outcome, changes in contraceptive practices and reasons for the changes, and particulars of any referrals to hospital either as an outpatient or an inpatient. Diagnoses on discharge from hospital are confirmed by obtaining copies of discharge letters or summaries. Women who stop attending the clinic sent are sent a postal version of the follow-up form and, if this is not returned, are interviewed by telephone or at home. The work at each clinic is co-ordinated by a part-time research assistant, and follow-up has been maintained with an annual loss rate for 'relevant' reasons (withdrawal of co-operation or loss of contact) of only about 0·4%.

On reaching the age of 45, each woman is allocated to one of three groups (a) oral contraceptives used for a total of 8 or more years, (b) oral contraceptives never used and (c) other durations of oral contraceptive use Only the women in the first two groups are followed up from then on in the detailed way described above.

The present analysis is limited to parous women (since IUCDs have been used by very few nulliparae during the study) with no known history of pelvic inflammatory disease. Woman-years of observation have been calculated in the groups being contrasted, using methods described previously (Vessey *et al* 1976). Women have been censored from the analysis at the time of occurrence of any of the following events: (a) end of follow-up, (b) loss to follow-up, (c) hospital referral for pelvic inflammatory disease and (d) hysterectomy or bilateral salpingectomy.

Episodes of pelvic inflammatory disease occurring during pregnancy or in the puerperium (that is, within 3 months of childbirth or abortion) are not considered here; corresponding periods of observation have been omitted from denominators. Likewise, a very small number of occurrences within 3 months of an abdominal or gynaecological operation have been excluded. The available clinical details of each of the remaining episodes were reviewed by H.B. (with assistance from L.V-M.) as far as possible in the absence of knowledge about the contraceptive history of the woman concerned. Episodes were divided into a number of subcategories, from which the following classification emerged:

(1) *Definite disease described as acute*

(a) Patients admitted to hospital with well-defined symptomatic tubal disease described as acute which was surgically confirmed at laparoscopy or laparotomy (34 cases).

(b) As for (a) but surgical confirmation not sought (27 cases) or with histologically proven septic endometritis (4 cases).

(2) *Definite disease not described as acute*

(a) Patients admitted to hospital with symptomatic tubal disease not described as acute which was surgically confirmed at laparoscopy or laparotomy (53 cases).

(b) As for (a), but discovered incidentally at a sterilizing operation, during investigation for infertility, or during some other surgical procedure (28 cases).

(3) *Other disease*

Patients seen in a hospital outpatient department and told they had the disease (49 cases) or admitted to hospital with an inconclusive clinical picture (11 cases). Since outpatient diagnosis are not routinely confirmed in the Oxford-Family Planning Association study and the women admitted as inpatients did not receive an operation, no more can be said about the diagnosis in patients in this category.

Bacteriological findings were incompletely recorded in discharge summaries and letters, and were of little help. Accordingly, as before, we have been unable to subdivide our cases of pelvic inflammatory disease according to the aetiological agent or agents.

Statistical analyses

Indirectly standardized rates have been calculated by the method described by Vessey *et al.* (1976) χ^2 tests for trend and for heterogeneity are based on the methods described by Breslow and Day (1987); 95% confidence intervals (CI) around point estimates of relative risk are based on methods described by the same authors

All the analyses described in the results section of this report were originally conducted separately for women up to 45 years of age and women over 45 years of age because of the change in study methods taking place at that age point. It was found, however, that the results obtained by considering the data as a whole did not differ in any important way from the results obtained in the subanalyses, and only the overall figures are presented here.

Results

We started the analysis by examining the association of age, parity, social class, cigarette smoking and age at first marriage with the risk of hospital referral for pelvic inflammatory disease, ignoring the influence of contraceptive method. There was no association of parity with risk (nullipara were, of course, excluded from the analysis) and this variable is not considered further. Next, we sought evidence of any temporal association with the rate of hospital referral for pelvic inflammatory disease, comparing the intervals 1968–73, 1974–78, 1979–83 and 1984–89; after allowing for confounding variables, no such association was found It was also found that closely similar results were obtained in all analyses when women with acute surgically confirmed disease (group 1a) were compared with women with acute non-surgically confirmed disease (group 1b), and likewise when women with non-acute surgically confirmed disease (group 2a) were compared with women with unsuspected disease discovered during operation for some other condition (group 2b) Accordingly, Tables 1–4 provide information only for acute, non-acute and other disease.

Table 1 shows that hospital referral for pelvic inflammatory disease was least common in the youngest and oldest age groups. There was also a modest tendency for referral for the disease to be most common in women of low social class (Table 2). Referral for non-acute disease was strongly positively associated with cigarette smoking; referral for 'other disease' barely showed this association at all while referral for acute disease occupied an intermediate position (Table 3). Referral for all three types of disease was negatively associated with age at first marriage; this trend was particularly clear for non-acute disease (Table 4).

In view of the above findings, it was decided to allow for the influence of age, social class, cigarette smoking and age at first marriage in all analyses of the effects of contraceptive methods (later, we also consider the effect that contraceptive method has on the association between pelvic inflammatory disease and the other four variables). Table 5 shows first hospital referral rates for acute pelvic inflammatory disease in relation to current use of various contraceptive

Table 1. First hospital referral rates per 1000 woman-years for pelvic inflammatory disease by age

Age (years)	Acute disease		Non-acute disease		Other disease		All disease	
	No.	Rate	No	Rate	No	Rate	No.	Rate
25–29	5	0·32	3	0·20	4	0·26	12	0·79
30–34	21	0·48	17	0·42	20	0·46	58	1·36
35–39	24	0·38	26	0·41	21	0·33	71	1·13
40–44	12	0·22	26	0·46	11	0·20	49	0·89
45+	3	0·09	9	0·27	4	0·13	16	0·49
Total	65	0·31	81	0·39	60	0·29	206	0·99

Rates are adjusted for the effects of social class (grouping as in Table 2), cigarette smoking (grouping as in Table 3) and age at first marriage (grouping as in Table 4).

$\chi^2_{(4)}$ Acute disease 11·1 ($P = 0{\cdot}02$)
Non acute disease 3·5 ($P = 0{\cdot}48$)
Other disease 9·3 ($P = 0{\cdot}06$)
All disease 16·4 ($P = 0{\cdot}002$)

methods; all ex-users of IUCDs have, however, been placed in a separate category. Current IUCD users have been divided into two groups—those using the older non-medicated devices (mostly Lippes Loops and Saf-T-Coils) and those using more modern medicated devices (mostly Cooper-7s and Copper Ts). For the calculation of relative risks, the reference group has been taken as women using 'other or no method' of contraception Clearly this is a heterogeneous group including those trying to get pregnant; those abandoning contraception; those relying on withdrawal, the safe period or chemicals; and those relying on vasectomy. Of these, the last mentioned is the most important, contributing nearly two-thirds of the woman-years of observation.

Although the numbers in Table 5 are generally small, the data suggest a protective effect of oral contraceptives, the diaphragm and female sterilization against hospital referral for pelvic inflammatory disease. Relative risks are markedly increased in current users of an IUCD but there is a strong suggestion that the older non-medicated devices (relative risk 7·6) are more at fault than the newer medicated devices (relative risk 2·7). There is little evidence of any enhanced risk of disease in ex-users of IUCDs (relative risk 1·2).

Table 6 corresponds exactly to Table 5 save that it considers non-acute pelvic inflammatory disease. The patterns seen are closely similar to those described previously, save that the range of variation in the rates is much less than for acute disease In addition, there is little difference between the rates for medicated and non-medicated IUCDs while rates in past users are only a little lower than those in current users.

Table 2. First hospital referral rates per 1000 woman-years for pelvic inflammatory disease by social class of women at entry to the study

Social class (Registrar General's classification)	Acute disease		Non-acute disease		Other disease		All disease	
	No	Rate	No.	Rate	No.	Rate	No.	Rate
I–II	20	0·27	25	0·36	22	0·29	67	0·92
III	35	0·31	47	0·42	25	0·23	107	0·97
IV–V (& others)	10	0·44	9	0·34	13	0·51	32	1·28
Total	65	0·31	81	0·39	60	0·29	206	0·99

Rates are adjusted for the effects of age (grouping as in Table 1), cigarette smoking and age at first marriage.

$\chi^2_{(1)}$ trend Acute disease 1·2 ($P = 0{\cdot}26$)
Non acute disease 0·0 ($P = 0{\cdot}89$)
Other disease 1·3 ($P = 0{\cdot}26$)
All disease 1·8 ($P = 0{\cdot}18$)

Table 3. First hospital referral rates per 1000 woman-years for pelvic inflammatory disease by cigarette smoking habits of women at entry to the study

Cigarette smoking (no. per day)	Acute disease		Non-acute disease		Other disease		All disease	
	No	Rate	No	Rate	No	Rate	No	Rate
None ever	32	0·28	32	0·28	28	0·25	92	0·81
Ex-smoker	7	0·28	6	0·26	7	0·28	20	0·82
1–14	10	0·25	14	0·36	17	0·43	41	1·04
15+	16	0·51	29	0·93	8	0·25	53	1·68
Total	65	0·31	81	0·39	60	0·29	206	0·99

Rates are adjusted for the effects of age, social class and age at first marriage

$\chi^2_{(1)}$ trend Acute disease 1·9 (P = 0·16)
Non acute disease 19·0 (P = 0·001)
Other disease 0·6 (P = 0·42)
All disease 15·5 (P = 0·001)

Other pelvic inflammatory disease is analysed in Table 7. The pattern is much like that in Table 6, but the relative risks are not elevated in either medicated IUCD users or in IUCD ex-users.

In view of the broad consistency of the findings in Tables 5–7, it was considered reasonable to put together the data for all types of pelvic inflammatory disease. The results are given in Table 8. The protective effect of oral contraceptives is now statistically significant while there is also considerable evidence of a protective effect of the diaphragm and female sterilization; use of the sheath, however, does not appear to confer such a benefit. Amongst IUCD users, non-medicated devices appear to be associated with almost twice the risk of medicated devices while there is little indication of any increase in risk in ex-users generally.

Next, we undertook an analysis of pelvic inflammatory disease in women who had used a Dalkon Shield. In total, 11 cases were discovered; four were classified as acute, five as non-acute and two as 'other disease'.

Six of the cases were in current users of a Dalkon Shield, three were in current users of another IUCD (with Dalkon Shield use in the past) while the remaining two were in current users of methods other than an IUCD (with Dalkon Shield use in the past). The data are summarized in Table 9. Among current users of an IUCD with exposure to a Dalkon Shield, the relative risk of hospital referral for pelvic inflammatory disease was 4·7 (95% CI 2·1–9·0) in comparison with current users of an IUCD without exposure to a Dalkon Shield.

First hospital referral rates for the three cate-

Table 4. First hospital referral rates per 1000 woman-years for pelvic inflammatory disease by age at first marriage

Age at first marriage (years)	Acute disease		Non-acute disease		Other disease		All disease	
	No	Rate	No	Rate	No.	Rate	No.	Rate
−17	5	0·49	6	0·58	6	0·78	17	1·78
18–19	14	0·31	18	0·40	16	0·37	48	1·08
20–21	25	0·37	31	0·47	12	0·19	68	1·03
22–23	11	0·23	17	0·35	14	0·28	42	0·86
24+	10	0·26	9	0·24	12	0·28	31	0·77
Total	65	0·31	81	0·39	60	0·29	206	0·99

Rates are adjusted for the effects of age, social class and cigarette smoking.

$\chi^2_{(1)}$ trend Acute disease 1·6 (P = 0·21)
Non acute disease 3·0 (P = 0·08)
Other disease 1·9 (P = 0·17)
All disease 6·4 (P = 0·01)

Table 5. First hospital referral rates per 1000 woman-years for acute pelvic inflammatory disease by contraceptive method

Current method	Use of IUCD	No	Rate	Relative risk	95% CI
Oral	Never	5	0·09	0·6	0·1– 2·7
Diaphragm	Never	3	0·12	0·8	0·1– 4·0
Sheath	Never	2	0·15	1·0	0·1– 6·0
Female sterilization	Never	2	0·12	0·8	0·1– 4·9
Other or none*	Never	5	0·15	1·0	—
IUCD—not medicated		42	1·13	7·6	3·0–24·7
IUCD—medicated		2	0·41	2·7	0·3–16·7
Any but IUCD	Past	4	0·18	1·2	0·2– 5·5

Figures are adjusted for the effects of age, social class, cigarette smoking and age at first marriage
*Reference group

gories of disease were also examined in relation to duration of current use of an IUCD. Women already using an IUCD at recruitment to the study were entered into this analysis at the point dictated by the duration of continuous prior use of the method (for example, a woman entering the investigation after 40 months of using an IUCD began to contribute woman-months of observation in the third duration of use group). There was no indication of any relation between risk of hospital referral for any type of pelvic inflammatory disease and duration of IUCD use (data not shown).

Finally, we returned to our original analyses of the effects of age, social class, cigarette smoking and age at first marriage and adjusted them for the influence of current use of an IUCD. Although the associations were generally slightly weakened. they none the less remained essentially as described in Tables 1–4.

Discussion

We undertook the present analysis in an attempt to take into account criticisms that have been levelled at earlier studies of the association between pelvic inflammatory disease and IUCD use. We recognise that the diagnosis of pelvic inflammatory disease is unreliable and subject to bias, but most of our acute cases, and all of our non-acute cases, were diagnosed operatively. Furthermore, the acute cases that were not diagnosed operatively were found to have closely similar characteristics to the operatively diagnosed cases during the analysis. For this reason

Table 6. First hospital referral rates per 1000 woman-years for non-acute pelvic inflammatory disease by contraceptive method

Current method	Use of IUCD	No.	Rate	Relative risk	95% CI
Oral	Never	6	0·13	0·4	0·1–1·2
Diaphragm	Never	5	0·22	0·7	0·2–2·1
Sheath	Never	5	0·34	1·1	0·3–3·3
Female sterilization	Never	7	0·40	1·3	0·4–3·5
Other or none*	Never	12	0·31	1·0	—
IUCD—not medicated		26	0·75	2·4	1·2–5·2
IUCD—medicated		5	0·73	2·3	0·6–7·1
Any but IUCD	Past	15	0·53	1·7	0·7–3·9

Figures are adjusted for the effects of age, social class, cigarette smoking and age at first marriage
*Reference group.

Table 7. First hospital referral rates per 1000 woman-years for other pelvic inflammatory disease by contraceptive method

Current method	Use of IUCD	No	Rate	Relative risk	95% CI
Oral	Never	7	0·13	0·4	0·1–1·2
Diaphragm	Never	4	0·14	0·4	0·1–1·5
Sheath	Never	7	0·44	1·4	0·4–3·8
Female sterilization	Never	0	0·00	—	—
Other or none*	Never	11	0·32	1·0	—
IUCD—not medicated		22	0·66	2·0	0·9–4·6
IUCD—medicated		2	0·29	0·9	0·1–4·1
Any but IUCD	Past	7	0·30	0·9	0·3–2·6

Figures are adjusted for the effects of age, social class, cigarette smoking and age at first marriage
*Reference group.

we considered it reasonable to combine the two groups of acute cases.

In this analysis, we have compared the risk of hospital referral for pelvic inflammatory disease in women using an IUCD, oral contraceptives, occlusive contraceptive methods and female sterilization with that in women using other methods or no method of contraception. We were aware of evidence that oral contraceptives (Rubin *et al.* 1982), occlusive contraceptives (Kelaghan *et al.* 1982) and female sterilization (Eschenbach *et al.* 1977) protect against pelvic inflammatory disease while it is, of course, well established that IUCDs increase the risk of such disease (World Health Organization Scientific Group 1987). Accordingly, we grouped users of the remaining contraceptive methods together, along with non-users of contraceptive methods, to provide a 'control group'.

Unfortunately, we do not have much information about the sexual behaviour of women in the Oxford Family Planning Association contraceptive study. The little that is available from a small sample of women who were specially interviewed (Wright *et al.* 1978) suggests that oral contraceptive users are the most likely to have had multiple sexual partners, closely followed by IUCD users with diaphragm users some way behind. We did, however, take into account two variables in the present analysis which show some correlation with sexual behaviour, namely cigarette smoking habits and age at first marriage. Thus there is evidence that cigarette smokers are more likely to have multiple sexual partners than non-smokers (Slattery *et al.* 1989) and that early age of first marriage is correlated with early age at first intercourse which is in turn correlated with an increased likelihood of having multiple sexual partners (Harris *et al.* 1980) Both these variables were found to be quite strongly predictive of the risk of hospital referral for pelvic inflammatory disease in our study in

Table 8. First hospital referral rates per 1000 woman-years for all pelvic inflammatory disease by contraceptive method

Current method	Use of IUCD	No	Rate	Relative risk	95% CI
Oral	Never	18	0·36	0·5	0·2–0·9
Diaphragm	Never	12	0·47	0·6	0·3–1·2
Sheath	Never	14	0·95	1·2	0·6–2·4
Female sterilization	Never	9	0·55	0·7	0·3–1·5
Other or none*	Never	28	0·79	1·0	—
IUCD—not medicated		90	2·57	3·3	2·3–5·0
IUCD—medicated		9	1·43	1·8	0·8–4·0
Any but IUCD	Past	26	1·04	1·3	0·7–2·3

Figures are adjusted for the effects of age, social class, cigarette smoking and age at first marriage
Reference group

Table 9. First hospital referral rates per 1000 woman-years for Dalkon Shield users and users of other intrauterine devices (IUCD)

Exposure category	No.	Rate	Rel. risk	95% CI
Current user of IUCD				
Never used Dalkon Shield*	90	2·3	1·0	—
Used Dalkon Shield	9	10·8	4·7	2·1–9·0
Ex-user of IUCD				
Never used Dalkon Shield	24	1·0	1·0	—
Used Dalkon Shield	2	1·8	1·8	0·2–7·2

Figures are adjusted for effects of age, social class, cigarette smoking and age at first marriage.
*Reference groups

the expected direction. It may be, of course, that these variables are not merely reflecting the effect of sexual behaviour but that they also have some influence on the risk of disease in their own right. It is impossible to determine whether or not this is so from the present study.

Finally, we have been at pains in the present analysis to distinguish the effects of newer medicated intrauterine devices from those of older non-medicated devices. We have also separated out the effects of Dalkon Shield use from those of other devices since it is well established that the Dalkon Shield is particularly prone to cause pelvic inflammatory disease (Lee *et al.* 1983).

These special features of our analysis greatly increase its value in comparison with the one we reported earlier (Vessey *et al.* 1981). By and large, the findings fit in well with those described in the more recent literature summarized by the World Health Organization Scientific Group (1987). Thus we have found a protective effect of oral contraceptive use, diaphragm use and female sterilization against hospital referral for pelvic inflammatory disease. We have also found an increased risk of such referral in current users of an IUCD and an especially high risk associated with a history of Dalkon Shield use. The strong indication that hospital referral for pelvic inflammatory disease is about twice as high in users of the older non-medicated devices than in users of the modern medicated devices is of particular interest as is the modest level of enhanced risk found in ex-users. The first of these findings is supported by the results of two studies on infertility which reported lower risks of tubal occlusion in users of copper-containing devices than in users of unmedicated devices (Daling *et al.* 1985; Cramer *et al* 1985). Another important feature of our results is that they make it quite clear that there is an increased risk of pelvic inflammatory disease in parous married women, some authors have suggested that the risk is largely concentrated in unmarried (and usually nulliparous) women (Lee *et al.* 1988). There are two surprising findings. First, there is no evidence in this analysis of a protective effect of condom use; this, perhaps, reflects the play of chance. Secondly, in contrast with our earlier analysis, we have found no evidence that the increased risk of acute pelvic inflammatory disease is especially concentrated during the early months of use of an IUCD We must, however, stress the fact that our study is not adequate for assessing the possible relation between replacement of an IUCD and the occurrence of disease since changes of device where removal is followed by immediate replacement with a device of the same type are not routinely recorded.

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The use of obstetric analgesia in Sweden 1983–1986

EVA GERDIN, SVEN CNATTINGIUS

Summary. The use of obstetric analgesia was investigated in a Swedish population-based prospective study of 335 207 births, which represents almost all women who had vaginal deliveries in Sweden between 1983 and 1986. Lumbar epidural analgesia (EDA) was used in 16%, paracervical block (PCB) in 12%, pethidine or morphine in 49% and pudendal block in 62%. All four types of analgesia were much more commonly used by nulliparae than multiparae. Variables such as maternal age, smoking, nationality, relationship with the infant's father and gestational age had only moderate influence on the rates of different types of analgesia. EDA and PCB were more frequently used in larger than in smaller hospitals and in the daytime than at night. No such differences were found for pethidine or morphine, or pudendal block, which were administered routinely by midwives.

'Based on present evidence, no mother should be allowed to suffer through labour and delivery unmedicated unless it is her specific desire' (R. J. Palahnuik, A. S. A. Lecture 1979).

For numerous women labour is their first experience of severe pain and for many it will be the most painful event in their lives. In a Swedish study comprising 544 women, it was found that 64% suffered severe to almost unbearable pain during labour and delivery (Bundsen *et al.* 1982). This figure is consistent with the finding in a Canadian study that only 9% of nulliparae and 24% of multiparae experienced mild pain and did not need any type of analgesia (Melzak *et al.* 1981).

During recent decades there has been much concern among women about the possible long-term effects on the fetus of drugs administered during labour. There has been a tendency to favour 'natural childbirth', free from technical assistance and drugs. However, most women require some form of pain relief during labour (Bundsen *et al.* 1982, Melzak *et al.* 1981).

The perception of pain during labour is subject to numerous influences, with wide individual variations related to a number of psychosocial, psychological and environmental factors. Parity has also been considered to influence the perception of pain during labour. Melzak *et al* (1981) found that nulliparae had a significantly higher perception of pain than multiparae, whereas Bundsen *et al.* (1982) found no difference between such groups Other variables such as socio-economic status, education level and age have been reported to be negatively correlated with intensity of labour pain experience (Davensport-Slack & Boylan 1974, Nettelbladt *et al.* 1976, Melzak *et al* 1981).

In 1973 a Medical Birth Registry was established by the National Board of Health and Welfare in Sweden (Karlberg 1980) Since 1982 information has been collected prospectively for each pregnancy, from the first antenatal visit to delivery, by the Registry. A study was undertaken to investigate the relation between the use of different forms of obstetric analgesia and vari-

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ables which have been considered to affect the perception of pain during labour.

The influence of the time of delivery and the routines in hospitals of different sizes on the type of analgesia used was also analysed.

Subjects and methods

The Swedish Medical Birth Registry

The Medical Birth Registry receives reports on births from all hospitals. These include demographic data and information on the previous reproductive history, complications during pregnancy, delivery and the neonatal period, and the type of obstetric analgesia administered. All births reported to this registry are validated every year against the Population Registry, Statistics, Sweden. The latter registry receives information on all newborn infants from the different parishes, and cross-checking is done with the aid of the mother's personal identification number The Medical Birth Registry covers more than 99% of all births in Sweden (Ericsson *et al.* 1984).

Recently, a quality control study of the Medical Birth Registry was undertaken. Except for parity, the information on all variables included in that study was considered to be of high quality (S. Cnattingius *et al.* unpublished observations). In the present study, information about parity was therefore collected from the Population Registry.

During the four years, 1983 to 1986, covered by this study, the number of women with vaginal deliveries reported to the Medical Birth Registry was 335 448. The study was restricted to women between 15 and 44 years of age For 241 women

[redacted]

assessing the extent of use of nitrous oxide-oxygen during delivery and the fact that the registry does not distinguish between the postpartum use of local infiltration analgesia and its use during delivery.

Independent variables

Parity was defined as the number of previous live births plus stillbirths. Nulliparae were those who had had no previous births and multiparae were those with at least one previous birth

The women were classified as smokers (those who generally smoked daily) and non-smokers.

The woman's relationship with the infant's father was recorded as whether she was living with him or not. Information about her relationship with the father and her smoking habits was obtained by midwives at the woman's first visit to the antenatal care unit

The women were classified by nationality into two groups, one comprising those from the Nordic countries (Sweden, Finland, Norway, Iceland and Denmark) and the other comprising immigrants from elsewhere.

Gestational age at delivery was categorized as preterm (defined as less than 37 weeks gestation) or full-term.

The day of delivery was designated either a working day or a holiday Holidays included Saturday, Sunday and every public holiday.

The time of delivery was also included as an independent variable

Maternity hospital organization

Sweden has 26 counties. Each county is a well-defined geographical and administrative unit, which governs its own provision of antenatal and

Table 1. Number of parturients and the use of obstetric analgesia by parity, maternal age, gestational age, smoking habits, family situation, nationality, type of hospital and time of delivery in Sweden 1983–1986

		Use of obstetric analgesia (%)			
Variable	No (%) of parturients	EDA	PCB	Pethidine/ morphine	Pudendal block
Parity					
Nulliparae	135 116 (40)	28	13	66	70
Multiparae	199 511 (60)	7	11	38	57
NK	580 (—)	—	—	—	—
Maternal age at delivery (years)					
15–19	11 597 (3)	29	13	66	66
20–24	81 799 (24)	20	13	58	65
25–29	124 936 (37)	15	12	49	64
30–34	81 741 (24)	12	11	43	60
35–39	30 727 (9)	11	10	40	56
40–44	4 407 (1)	10	9	39	51
Gestational age (weeks)					
≥37	318 174 (95)	16	12	50	63
<37	16 350 (5)	17	9	44	56
NK	683 (—)	—	—	—	—
Smoking habits					
Non-smoker	218 552 (65)	15	12	48	63
Daily smoker	94 038 (28)	18	12	52	61
NK	22 617 (7)	18	11	48	61
Living with infant's father					
Yes	304 220 (91)	15	12	49	63
No	17 558 (5)	23	11	58	60
NK	13 429 (4)	17	11	47	58
Nationality					
Nordic countries	318 778 (95)	16	12	49	63
Others	16 429 (5)	17	9	55	53
Type of hospital					
Regional	74 284 (22)	19	11	51	61
Central	198 687 (59)	16	14	47	62
County, specialized	46 233 (14)	12	8	58	69
County, non-specialized	15 756 (5)	4	1	42	50
NK	247 (—)	—	—	—	—
Delivery day					
Working days	242 384 (72)	16	12	49	62
Holidays	92 725 (28)	15	11	50	63
NK	98 (—)	—	—	—	—
Delivery time					
24.00–05 59 hours	82 008 (24)	12	9	48	61
06 00–11.59 hours	81 286 (24)	12	11	47	64
12 00–17.59 hours	94 565 (28)	18	14	51	63
18.00–23 59 hours	77 305 (23)	21	12	51	62
NK	43 (—)	—	—	—	—
Total	335 207 (100)	16	12	49	62

EDA = epidural lumbar analgesia, PCB = paracervical block, NK = not known.

chosen according to their place of residence at the time of delivery. Overall, 99% of the women living in the catchment area or referral district of a central hospital were delivered at that hospital and only 3–14% of those living in the catchment area of a county hospital used hospitals other

Table 2. Predicted rates (%) of obstetric analgesia in nulliparae in Sweden 1983–1986, based on a logistic regression model

Variable	EDA	PCB	Pethidine/ morphine	Pudendal block
Maternal age at delivery (years)				
15–19	26 s	14	66 s	70 s
20–24	24	15	65 s	72
25–29*	23	14	63	73
30–34	26 s	13	61 s	71 s
35–44	28 s	12 s	59 s	69 s
Gestational age (weeks)				
≥37*	23	14	63	73
<37	20 s	9 s	50 s	69 s
Smoking habits				
Non-smoker*	23	a	63	73
Daily smoker	27 s		65 s	71 s
Living with infant's father				
Yes*	23	14	a	73
No	25 s	12 s		68 s
Nationality				
Nordic countries*		14		73
Others	a	11 s	a	62 s
Type of hospital				
Regional	27 s	12 s	67 s	71 s
Central*	23	14	63	73
County, specialized	19 s	8 s	74 s	79 s
County, non-specialized	7 s	1 s	63	66 s
Delivery day				
Working days*	23	a	63	a
Holidays	22 s		64 s	
Delivery time				
24.00–05.59 hours*	23	14	63	73
06.00–11.59 hours	20 s	15 s	61 s	75 s
12.00–17.59 hours	28 s	18 s	62	72
18.00–23.59 hours	33 s	17 s	62	71 s
Total	123 480	129 532	125 840	123 480

a = The variable was not included in the analysis because of lack of significance.
s = $P<0{\cdot}001$.
* Denotes the reference group
EDA = epidural lumbar analgesia, PCB = paracervical block

than their own county hospital (Eksmyr 1986). Consequently, very few women were referred to larger hospitals for their delivery.

Statistical analysis

Multiple logistic regression analysis was undertaken to estimate the effects of different independent variables on the four types of analgesia used (Schlesselman 1982). The independent variables were maternal age, parity, smoking habit, relationship with the infant's father, nationality, gestational age, type of hospital and time of delivery. Initially all these variables were included in the analysis. However, because of the very large number of women and the frequency of use of obstetric analgesia, even small absolute differences would have been statistically significant. Therefore, in the final models only variables with strong statistical significance ($P<0{\cdot}001$) were included in the analysis. The continuous variables were categorized so as to avoid dubious assumptions concerning linearity.

For statistical analysis the SAS program package (SAS Institute; SAS user's guide, basics and statistics, 1985) was used.

Results

Table 1 shows the number of women who

Table 3. Predicted rates (%) of obstetric analgesia in multiparae

Variable	EDA	PCB	Pethidine/ morphine	Pudental block
Maternal age at delivery (years)				
15–19	5·6	10	37	54
20–24	4·6	11	37 s	57 s
25–29*	4·4	10	35	59
30–34	4·7	9 s	33 s	59
35–44	5·1 s	9 s	33 s	55 s
Gestational age (weeks)				
≥37*	4·4	10	35	59
<37	5·6 s	8 s	33 s	51 s
Smoking habits				
Non-smoker*	4·4	a	35	59
Daily smoker	5·1 s		38 s	56 s
Living with infant's father				
Yes*	4·4	a	35	59
No	5·1 s		41 s	55 s
Nationality				
Nordic countries*	a	10	35	59
Others		8 s	42 s	48 s
Type of hospital				
Regional	5·2 s	8 s	38 s	58 s
Central*	4·4	10	35	59
County, specialized	2·8 s	5 s	46 s	67 s
County, non-specialized	1·1 s	1 s	30 s	43 s
Delivery day				
Working days*	4·4	10	a	a
Holidays	3·7 s	9 s		
Delivery time				
24.00–05.59 hours*	4·4	10	35	59
06.00–11 59 hours	5·2 s	13 s	34 s	62 s
12.00–17 59 hours	8·9 s	18 s	39 s	61 s
18.00–23.59 hours	8·2 s	15 s	35	60
Total	182 938	199 036	182 938	182 938

a The variable was not included in the analysis because of lack of significance.
s = $P<0{\cdot}001$.
* Denotes the reference group.
EDA = epidural lumbar analgesia, PCB = paracervical block

received the four different types of analgesia, distributed by the independent variables included in the analyses. EDA was given to 16% and PCB to 12%; pethidine or morphine was given to 49%, and a pudendal block to 62%. EDA and PCB were very seldom given in combination: only 6% of those women who were given PCB also received EDA. Only 1·5% of the women were reported to have had no analgesia (not even nitrous oxide-oxygen or local infiltration) during labour and delivery, or after delivery.

The use of obstetric analgesia varied mainly with the type of hospital, time of delivery and parity. Maternal characteristics such as age, smoking and relationship with the infant's father also influenced the rates of obstetric analgesia. Parity varied mainly with maternal age, but also with the family situation. Overall 8% of nulliparae were teenagers, compared with only 0·5% of multiparae; 8% of nulliparae and 3% of multiparae were not living with the infant's father. To take such factors into consideration, a multivariate approach was used. Because of the great differences between nulliparae and multiparae in the use of pain relief, the analyses were preceded by stratification with respect to parity (Tables 2 and 3). The reference group chosen, both for nulliparae and for multiparae, represented an estimate of the most common delivery

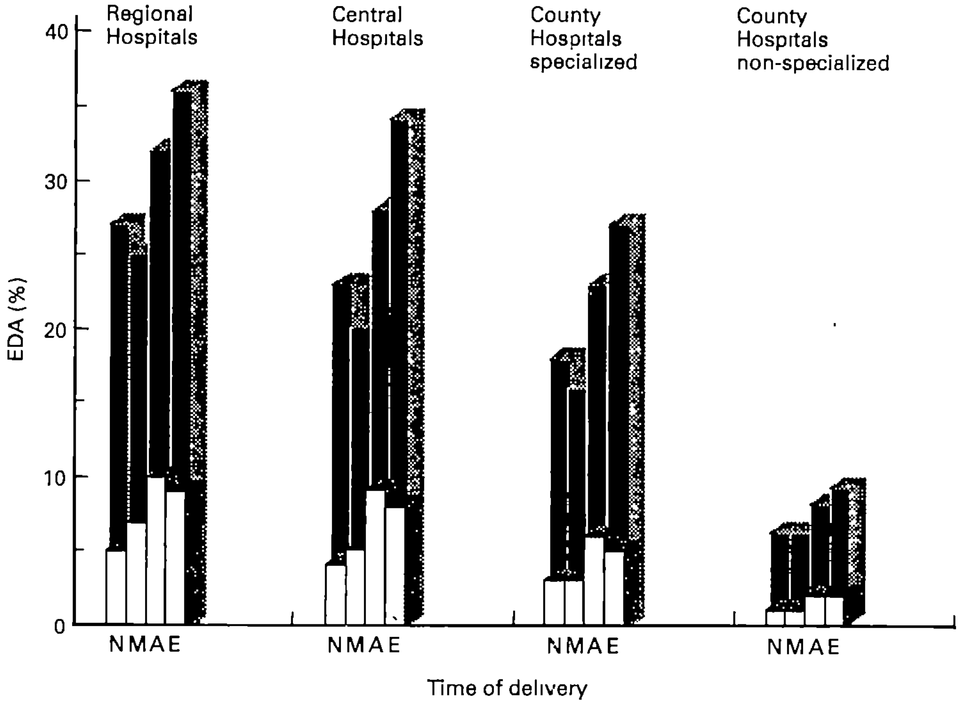

Fig. 1. Frequency of use of epidural lumbar analgesia (EDA) (%) at various types of hospital in relation to time of delivery among nulliparae (black bars) and multiparae (white bars) in Sweden, 1983–1986 N = Night, 24.00–05 59 hours; M = Morning, 06 00–11 59 hours; A = Afternoon, 12 00–17 59 hours; E = Evening, 18 00–23.59 hours.

situation, that is a non-smoking, cohabiting Nordic woman, aged 25–29 years, delivered between midnight and 05·59 hours on a working day in a central hospital after 36 weeks' gestation.

As seen in Tables 2 and 3, the highest frequency of EDA was found among the youngest and oldest of both the nulliparous and parous groups. Among smokers and among women not living with the infant's father, the use of EDA was slightly higher than that in the reference group. There were hardly any differences in the use of obstetric analgesia between women from the Nordic countries and those from other countries. There was virtually no difference in the use of analgesia between working days and holidays. Parous women were more likely to have EDA and less likely to have other types of analgesia if preterm labour was a factor (Table 3).

Overall 30% of all women who were delivered in regional and central hospitals received either EDA or PCB (Table 1). There were, however, great differences between smaller and larger hospitals in the use of EDA and PCB. For example, among nulliparae the rate of EDA ranged from 7% in non-specialized county hospitals to 27% in regional hospitals (Table 2). Such major differences between different types of hospital were not found for pethidine or morphine analgesia, or pudendal block There was a clear variation in the use of EDA and PCB with the time of day. The temporal variation in the use of EDA in all four types of hospital was analysed and is depicted in Figure 1. Regional hospitals showed less time variation in EDA than the other hospitals ($P<0·001$).

Discussion

A higher frequency of requests for obstetric analgesia by nulliparae than by multiparae does not necessarily reflect greater perception of pain. Multiparae, with their shorter duration of labour (Bundsen *et al.* 1982), may experience the highest pain intensity during the second stage and the delivery (Fällman *et al.* 1974), when analgesia is generally withheld.

The surprisingly low frequency (1·5%) of women not requiring any analgesia may be partly explained by the registration protocol for use of analgesia during childbirth which includes local infiltration analgesia for postpartum procedures, such as repair of perineal trauma. Also, even very short term use of nitrous oxide-oxygen is registered as obstetric analgesia

It has been suggested that different ethnic groups vary significantly in their response to pain (Zborowski 1952; Zola 1966). The widely held image of Nordic women quietly concealing their childbirth pain, in contrast to the supposedly more expressive women of other ethnic origins, was not substantiated by greater utilization of obstetric analgesia among immigrants from outside the Nordic countries in this study.

Parous women delivered preterm received EDA more often than those delivered at term One explanation for this may be the avoidance of narcotic analgesics and PCB because of fear of adverse effects on the preterm infant The difference was not related to local hospital factors, as it was similar in all four types of hospital.

The investigation revealed considerable differences in the frequency of EDA and PCB administration, depending on the time of day of delivery and the type of hospital. The simplest forms of analgesia, parenteral morphine or pethidine and pudendal block, are administered by midwives, on their own intiative, without specific prescription by an obstetrician. If PCB is considered necessary, it is generally administered by the obstetrician in charge, and EDA is given by an anaesthetist. The midwife, who is close to the woman throughout labour, is able to give some analgesic support but the most effective form of analgesia, EDA (Scott 1977), is given by a specialist who, out of office hours, has a number of other emergency duties. In the present study women giving birth at night or in the morning, who would have required their EDA to be administered during the evening or the night, received this form of analgesia less frequently than women delivered in the afternoon or evening. Although all hospitals had anaesthetists available on a 24-h basis, women giving birth at night clearly received or required EDA less frequently than during the daytime. In contrast, pethidine or morphine and pudendal block, administered by the midwife, had an even distribution during the night and day.

The temporal variation in the use of EDA and PCB was similar every day of the week. This may be explained by a greater capacity for obstetric and anaesthetic service in the daytime than at night, during both working days and holidays.

Differences in the type of analgesia used in labour in different categories of hospitals cannot be explained by medical reasons alone. Few women are referred from county hospitals to a regional or central hospital for delivery; for most women who are transferred between hospitals it is the anticipation of need for special neonatal care, rather than maternal complications during labour, which prompts referral

Local medical resources may determine differences in frequency of use of obstetric analgesia.They may also reflect different attitudes towards pain relief among women in the different types of hospitals Women giving birth at a county hospital may have lower expectations and may, therefore, demand analgesia less often than those delivered at a regional or central hospital.

Many women regard the geographical proximity of a local maternity hospital to be more important than the availability of effective pain relief in labour at a larger, more distant hospital. In a Swedish investigation (Fallman *et al.* 1974) more than half the women questioned had an ambivalent or negative attitude towards travelling 50–100 km to obtain effective pain relief.

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Middle cerebral artery flow velocity waveforms in fetal hypoxaemia

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Summary. In 81 small-for-gestational age fetuses (SGA) colour flow imaging was used to identify the fetal middle cerebral artery for subsequent pulsed Doppler studies. Impedence to flow (pulsatility index; PI) was significantly lower, and mean blood velocity was significantly higher, than the respective reference ranges with gestation. Fetal blood sampling by cordocentesis was performed in all SGA fetuses and a significant quadratic relation was found between fetal hypoxaemia and the degree of reduction in the PI of FVWs from the fetal middle cerebral artery. Thus, maximum reduction in PI is reached when the fetal PO_2 is 2–4 SD below the normal mean for gestation. When the oxygen deficit is greater there is a tendency for the PI to rise, and this presumably reflects the development of brain oedema.

Animal studies have shown that fetal hypoxaemia is associated with a relative redistribution of cardiac output resulting in preferential perfusion of the brain at the expense of the viscera (Cohn *et al.* 1974; Peeters *et al.* 1979). The aim of the study was to investigate this brain-sparing effect in human fetuses by relating umbilical cord blood gases, in samples obtained by cordocentesis, with Doppler indices of velocity and impedence to flow in the fetal middle cerebral artery.

Subjects and methods

Flow velocity waveforms (FVW) were obtained from the middle cerebral artery and measured on one occasion in 81 small-for-gestational age fetuses (SGA) at 19–38 weeks gestation and 162 appropriate-for-gestational age fetuses (AGA) at 18–42 weeks gestation. Gestational age was calculated from Naegele's rule and was confirmed by an ultrasonographic measurement of the fetal biparietal diameter at 16–20 weeks' amenorrhoea

The 81 pregnancies with SGA fetuses were referred to our unit for cordocentesis for fetal karyotyping and blood gas analysis. In all pregnancies the fetal abdominal circumference was below the 2·5th centile of our reference range for gestation, which was constructed from the study of 1610 pregnancies. The Doppler studies were undertaken up to 30 min before cordocentesis, which was performed without maternal sedation or fetal paralysis (Nicolaides *et al.* 1986). The umbilical cord vessel was identified as either artery or vein by the ultrasonographically detectable turbulence produced after the intravascular injection of 0·4 ml normal saline. The umbilical artery was sampled in 12 fetuses and the umbilical vein in 69. Fetal blood gases were measured by an automated blood gas analyser (Radiometer ABL 330, Copenhagen, Denmark) All fetuses included in this study were morphologically and karyotypically normal

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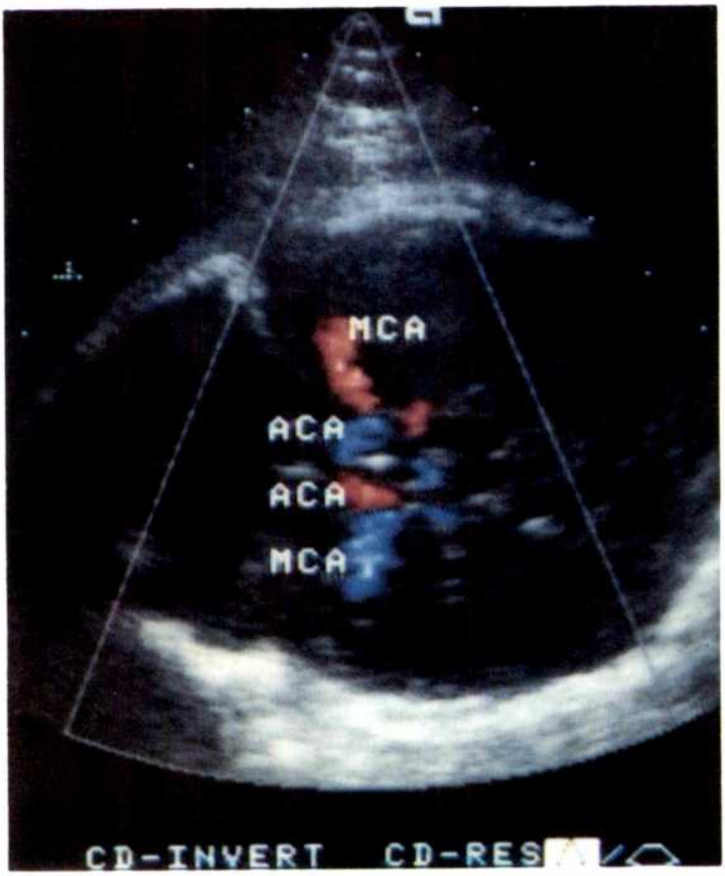

Fig. 1. Colour flow imaging of the fetal intra-cranial vasculature demonstrating by the anterior (ACA) and middle cerebral (MCA) arteries.

Reference ranges of the Doppler variables with gestational age were obtained from the cross-sectional study of 162 AGA fetuses. The women were recruited from the routine antenatal clinic and had uncomplicated singleton pregnancies. An ultrasound scan performed at the time of the Doppler study showed all fetuses to be morphologically normal and the head and abdominal circumferences to be between the 2·5th and 97·5th centiles of our reference ranges for gestation.

Colour flow imaging was used to identify the fetal middle cerebral artery for subsequent pulsed Doppler studies (Acuson 128, Acuson, California, USA; 5 MHz linear array and 3·5 MHz sector transducers). The high pass filter was set at 125 Hz and the transmitted power output level, in the low power output mode used throughout the study, was 36 and 50 mW/cm^2 SPTA in colour and pulsed Doppler modes respectively. During the studies care was taken to apply minimal pressure to the maternal abdomen with the transducer, as fetal head compression is associated with alterations of intra-cranial arterial FVWs, (Vyas *et al.* 1989).

For Doppler studies the woman was placed in a semi-recumbent position and a transverse view of the fetal brain was obtained at the level of the biparietal diameter. The transducer was then moved towards the base of the skull at the level of the lesser wing of the sphenoid bone. Using colour flow imaging, the middle cerebral artery could be seen as a major lateral branch of the circle of Willis running anterolaterally towards the lateral edge of the orbit (Fig. 1). The pulsed Doppler sample gate was then placed on the proximal portion of this vessel to obtain FVWs. The angle of vessel insonation was 0–35° and the Doppler gate size was 4–6 mm. All Doppler studies were performed in the absence of gross fetal body or breathing movements (Marsal *et al.* 1984).

The FVWs were analysed by an on-line spectrum analyser (Doptek, Doptek, UK) when

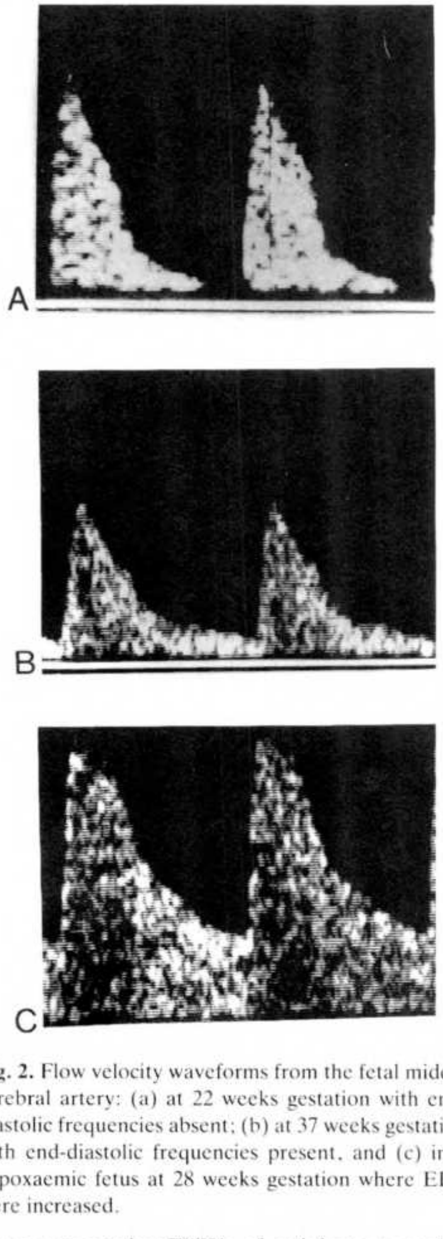

Fig. 2. Flow velocity waveforms from the fetal middle cerebral artery: (a) at 22 weeks gestation with end-diastolic frequencies absent; (b) at 37 weeks gestation with end-diastolic frequencies present, and (c) in a hypoxaemic fetus at 28 weeks gestation where EDF were increased.

three consecutive FVWs of satisfactory quality had been obtained. To compute the pulsatility index (PI) the maximum frequency envelope of the FVW was outlined using a light pen. The time-averaged intensity-weighted mean blood velocity (Vm) was calculated after the angle of vessel insonation had been determined from the frozen image. The mean value of three FVWs was recorded for all further analyses. The PI was measured in all 81 SGA and 162 AGA fetuses. However, the fetal middle cerebral artery Vm was measured only in the last 58 SGA and 106 AGA fetuses because the software required to calculate this variable was unavailable in the earlier part of the study.

The intra-observer coefficients of variation for the measurement of Vm and PI of FVWs from the fetal middle cerebral artery were determined by performing 10 consecutive examinations on three AGA fetuses within a 1-h period. These were 5·3% for the measurement of PI and 11·1% for the measurement of Vm.

Statistical analysis

For the AGA group, reference ranges (mean, 2·5th and 97·5th centiles) of the Vm and PI of FVWs from the fetal middle cerebral artery with gestation were derived by regression analysis (Statistics package for personal computers, Timberlake Clark Ltd, 40b Royal Hill, London SE10).

Because in normal fetuses blood PO_2, PCO_2, pH (Nicolaides *et al.* 1989) and both Doppler variables change with gestation, the individual measurements in the SGA fetuses were expressed as the number of standard deviations (SD's) from the respective normal mean for gestation ($\triangle PO_2$, $\triangle PCO_2$, △pH, △PI and △Vm). The one sample Student's *t*-test was used to examine whether the mean △PI and △Vm of the SGA group were significantly different from zero.

Results

In the AGA group, the FVW is highly pulsatile and the presence of end-diastolic frequencies (EDF) becomes more common with advancing gestation. Thus, EDF were present in 32 of 43 (75%) fetuses at 18–25 weeks, 38 of 50 (76%) at 26–33 weeks and all 69 fetuses examined at >34 weeks gestation (Fig. 2). The relation of PI with gestation was best described by a quadratic equation (Fig. 3). The data on Vm were made Gaussian by $\log_{10}$ transformation and the relation with gestation was best described by a linear equation (Fig. 4). In the 106 fetuses in whom both PI and Vm were measured, there was a significant association between the two variables ($r = 0·67$, $P<0·0001$, constant = 25·92, slope = 6·454, residual SD = 4·012).

In the 81 SGA fetuses, the mean △PI (−2·035 SD) was significantly lower than zero (Fig. 5; $t_{80} = 22·23$, $P<0·0001$) and there was a significant relation between △PI and $\triangle PO_2$ (Fig. 6). Similarly, there was a significant relation

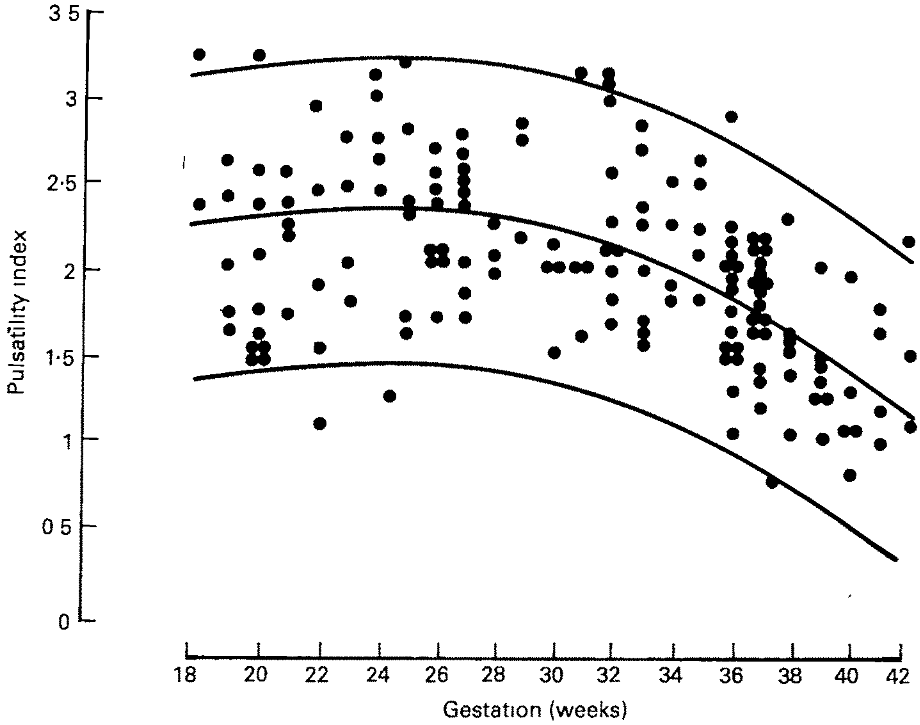

Fig. 3. Reference range (mean and individual 95% CI) of fetal middle cerebral artery pulsatility index with gestation, constructed from a cross-sectional study of 162 appropriate-for-gestational age fetuses (●) [$r = 0{\cdot}57$; $P<0{\cdot}0001$; constant $= -0{\cdot}611$; linear coefficient $= 0{\cdot}228$; quadratic coefficient $= -0{\cdot}004$; residual SD $= 0{\cdot}444$].

between ΔPI and ΔpH ($r = 0{\cdot}47$, $P<0{\cdot}01$, constant $= -1{\cdot}461$, linear coefficient $= 0{\cdot}358$, quadratic coefficient $= 0{\cdot}030$, residual SD $= 0{\cdot}732$).

In the 58 SGA fetuses, the mean ΔVm (2·045 SD) was significantly higher than zero (Fig. 7; $t_{57} = 12{\cdot}27$, $P<0{\cdot}0001$) and there were significant associations between ΔVm and ΔPO_2 (Fig. 8), and ΔVm and ΔpH ($r = 0{\cdot}491$, $P<0{\cdot}01$, constant $= 0{\cdot}763$, linear coefficient $= -0{\cdot}782$, quadratic coefficient $= -0{\cdot}074$, residual SD $= 1{\cdot}135$). In the 58 SGA fetuses in which both ΔPI and ΔVm were measured, there was a significant association between the two variables ($r = -0{\cdot}37$, $P<0{\cdot}01$, constant $= -1{\cdot}731$, slope $= 0{\cdot}200$, residual SD $= 0{\cdot}652$). There were no significant associations between ΔPCO_2 and ΔPI or ΔVm ($n = 81$, $r = -0{\cdot}05$ and $n = 58$, $r = -0{\cdot}05$ respectively).

Discussion

In normal pregnancy there is a gestation related fall in the PI, and by implication impedence to flow, in the fetal middle cerebral artery. This

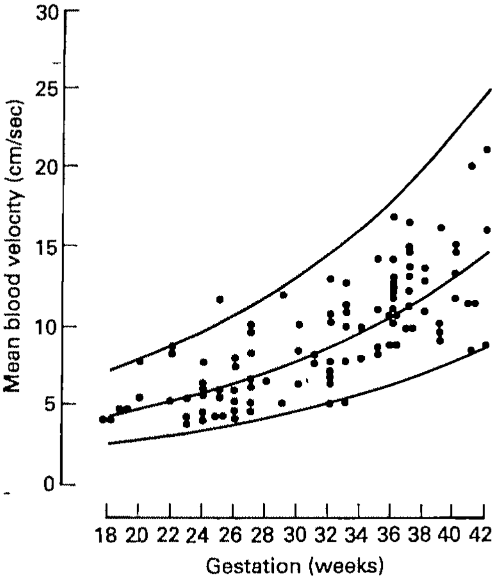

Fig. 4. Reference range (mean and individual 95% CI) of fetal middle cerebral artery mean blood velocity with gestation, constructed from a cross-sectional study of 106 appropriate-for-gestation age fetuses (●) [$r = 0{\cdot}79$; $P<0{\cdot}0001$; constant $= 0{\cdot}173$; slope $0{\cdot}023$; residual SD $= 0{\cdot}119$]

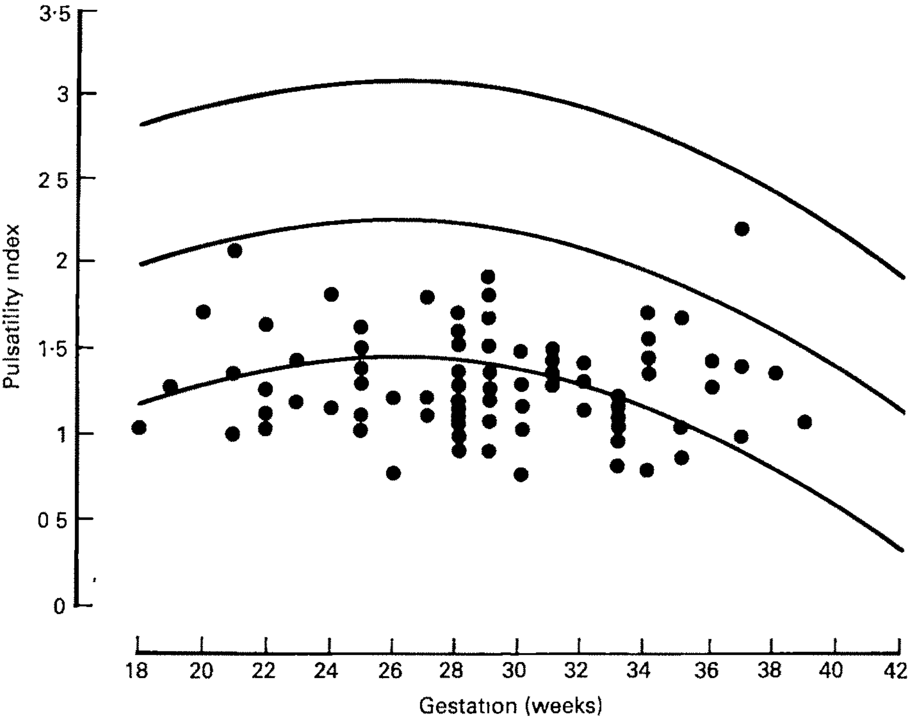

Fig. 5. Middle cerebral artery pulsatility index of the 81 SGA fetuses (●) plotted on the reference range.

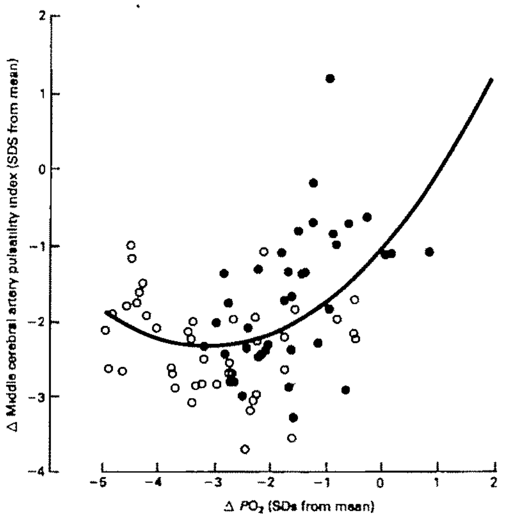

Fig. 6. The relation between fetal hypoxaemia and fetal middle cerebral artery pulsatility index, both expressed as the number of SD by which the observed values differed from the respective normal mean for gestation. The open circles indicate acidaemic fetuses and the closed circles represent non-acadaemic fetuses. [$r = 0{\cdot}46$; $P < 0{\cdot}001$; constant $= -1{\cdot}021$; linear coefficient $= 0{\cdot}844$, quadratic coefficient $= 0{\cdot}135$; residual SD $= 0{\cdot}740$].

finding is in agreement with those of Kirkinen *et al.* (1987) and Van Den Wijngaard *et al.* (1989) who examined 83 and 55 fetuses respectively at 25–41 weeks gestation. Both studies noted the

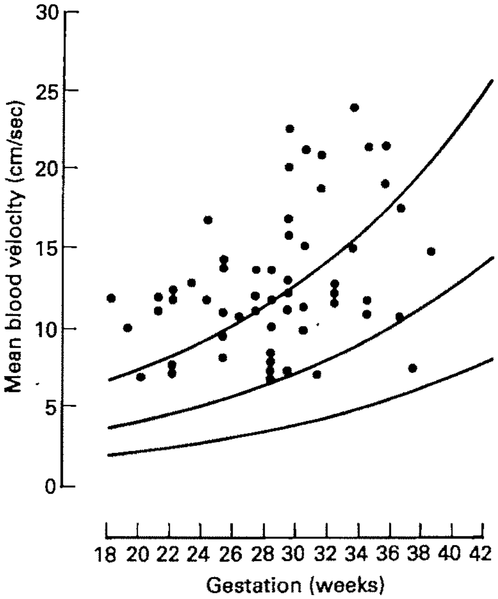

Fig. 7. Middle cerebral artery mean blood velocity of the 58 SGA fetuses (●) plotted on the reference range

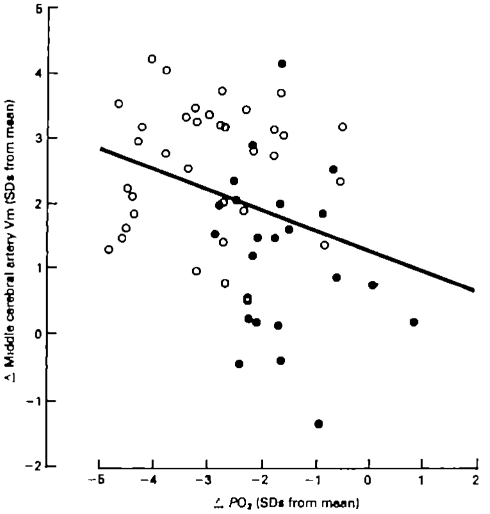

Fig. 8. The relation between fetal hypoxaemia and fetal middle cerebral artery mean blood velocity, both expressed as the number of SD by which the observed values differed from the respective normal mean for gestation. The open circles indicate acidaemic fetuses and the closed circles represent non-acidaemic fetuses [$r = -0{\cdot}31$, $P<0{\cdot}05$; constant= 1·279; slope = −0·311; residual SD = 1·216]

presence of EDF in all fetuses; in the current study, EDF were absent in 24% of the examinations at 26–33 weeks. This discrepancy may be due to the different high pass filters used; 100 Hz in their studies, compared with 125 Hz in the current study.

The PI of FVWs from the fetal common carotid artery falls with advancing gestation (Bilardo *et al.* 1988). The present study demonstrates that there is a similar fall in impedence to flow in the middle cerebral artery suggesting that changes in the common carotid artery, during normal pregnancy, are predominantly due to a reduction in impedence to flow in the cerebral vasculature.

The blood velocity increases with advancing gestation, and this increase is significantly associated with the decrease in PI. Mean blood velocity in the intracranial vasculature has not been reported previously, possibly due to difficulties in B-mode imaging and therefore accurate measurement of the angle of vessel insonation. This problem has been overcome by the use of colour flow imaging.

In SGA fetuses, the PI of FVWs from the fetal middle cerebral artery is reduced and the degree of this reduction is significantly related to the degree of fetal hypoxaemia. The PI of FVWs represents downstream impedence to flow (Gosling & King 1975) and our data provide evidence of vasodilatation in the cerebral vasculature during mild to moderate hypoxaemia. With severe degrees of hypoxaemia (2–4 SD below the normal mean for gestation), usually with associated acidaemia, the reduction in PI reaches a maximum which probably represents maximum vessel dilatation. In extreme hypoxaemia (>4 SD below the normal mean for gestation) the reduction in PI is proportionally less (Fig. 5). It could be hypothesized that in severely hypoxaemic SGA fetuses the vasodilatation mediated decrease in PI is blunted by increased intracranial pressure due to cerebral oedema. It has been shown that fetal head compression, and therefore increased intracranial pressure, is associated with an increase in the PI of FVWs from the middle cerebral artery (Vyas *et al.* 1990).

Blood velocity in the middle cerebral artery is higher in the SGA than the AGA group, and there are significant associations between the increased blood velocity and fetal hypoxaemia and acidaemia. However, the relation between the increase in mean blood velocity and the decrease in PI is weaker in SGA than AGA fetuses ($r = -0{\cdot}37$ and $r = -0{\cdot}67$ respectively). These findings suggest that in SGA fetuses blood velocity is not determined by downstream impedence to flow alone and that other factors, such as cardiac contractility, vessel compliance and blood viscosity may also play a role.

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Experience with a 'physiological' steroid replacement regimen for the establishment of a receptive endometrium in women with premature ovarian failure

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Summary. Eighteen women with a premature menopause underwent assessment of serial serum oestradiol (E2) and progesterone levels and endometrial histology and function. Patients received continuous transdermal E2, and progesterone either orally or vaginally for 14 days. Physiological levels of E2 were attained. Significantly higher levels of progesterone were achieved with vaginal progesterone ($P<0{\cdot}01$). Endometrial biopsies obtained during E2 replacement demonstrated normal proliferative features. Expression of an oestrogen related antigen (ER-Ag) was localized in the cytoplasm of the epithelium. After 3 days of progesterone replacement the endometrium showed normal secretory features and expression of ER-Ag in the stroma as well as in the glands. After 7 days of progesterone supplementation, vaginal administration produced a more consistent physiological appearance than oral administration. Thus transdermal E2 combined with vaginal progesterone is a highly satisfactory combination for establishing a physiological endometrium in women with premature ovarian failure.

Premature ovarian failure will affect a significant proportion of women attending infertility clinics. Coulam *et al.* (1986) reported a prevalence of 1–3% in the general population. Over the last 3 years, the donation of oocytes with assisted reproduction techniques has offered these young women with previously irreversible sterility the hope of pregnancy (Lutjen *et al.* 1984; Asch *et al.* 1988; Abdalla *et al.* 1989). Essential to this objective is the establishment and maintenance of a receptive endometrium. We have assessed the relation between serum oestradiol and progesterone levels and serial endometrial histology and function in a group of women with premature ovarian failure.

Several different sequential steroid replacement regimens and delivery routes have been described. The most popular mode and route of replacement is oral oestrogen and intramuscular progesterone (Lutjen *et al.* 1984; Asch *et al.* 1988). Oral oestrogen undergoes first pass metabolism by the liver and exposes the liver to high oestrogen levels, while daily injections are inconvenient. As an alternative we have assessed transdermal oestradiol (E2) delivery (Estraderm 50, Ciba-Geigy) and both oral

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micronized progesterone (Utrogestan, Besins Iscovesco, Paris, France) and vaginal progesterone (pessary 50 mg twice daily and micronized 100 mg thrice daily) as modes of steroid supplementation. Successful pregnancy has been reported by Salat-Baroux *et al.* (1988), using transdermal E2 and vaginal micronized progesterone; oral micronized progesterone was also used successfully by Devroey *et al.* (1988). Recently, transdermal E2 has been considered comparable to oral E2 for steroid replacement (Droesch *et al.* 1988). These authors examined endometrial histology in the peri-implantation and late luteal phase and commented upon a significant disparity between the glandular and stromal components in the peri-implantation period, which did not appear to be an impediment to implantation. Progesterone was administered intramuscularly.

We have assessed endometrial response with routine histology, applying the criteria of Noyes *et al.* (1950). In addition, we have examined the expression of an oestrogen receptor related antigen (ER-Ag) in the endometrial glands and stroma. We have thus examined critically for the first time the relation between steroid levels and quality of endometrial histology, in women with premature ovarian failure treated with transdermal oestradiol and oral or vaginal progesterone.

Subjects and methods

Eighteen women with premature ovarian failure presented to the reproductive endocrine clinic and were entered into an ovum donor programme. Their clinical details are summarized in Table 1. None had demonstrable antiovarian antibodies. The reference range for ovulating women was obtained from 60 infertile women studied by hormonal and ultrasound assessment three times weekly, and found to have ovulated by all the standard criteria (Buckler *et al.* 1989).

Oestradiol (Estraderm 50) supplementation was increased from a maintenance dose of one patch in a stepwise fashion to three patches and these were changed twice weekly. Progesterone administration was started 14 days after the start of E2 replacement as (i) oral micronized progesterone in 10 women (100 mg thrice daily) (ii) vaginal pessary in four women (50 mg twice daily) or (iii) micronized vaginal progesterone in 10 women (100 mg thrice daily). Serum samples were collected three times weekly for E2 and progesterone radioimmunoassay, throughout a 28 day period of steroid supplementation. Radioimmunoassay of serum E2 was by a specific kit method using ^{125}I-labelled E2 (Coat-A-Count, Diagnostic Products Corp, Los Angeles, CA); and progesterone was assayed by a direct method as described by Ratcliffe *et al.* (1982).

To assess biological response, serial endometrial biopsies were taken after 10 or 11 days of E2 replacement in 19 women and again after 3 days (oral, $n = 4$; pessary, $n = 4$; micronized vaginal, $n = 7$) and 7 days (oral, $n = 5$; pessary, $n = 4$; micronized vaginal $n = 6$) after the beginning of progesterone administration. Serial biopsies were conducted as out-patient procedures without the need for analgesia with either a Sharman (Chas F. Thackray Ltd, Leeds, England) or a Roussel-Gynocheck curette. In order to avoid sampling the same site on more than one occasion samples were taken from the left anterior fundal, posterior fundal and right anterior fundal regions on days 10 or 11, 18 and 22 of the study cycle respectively. Biopsies for histological assessment were fixed in Bouin's solution and those for immunohistochemistry in methacarn for 40 min and transferred to 70% alcohol and thereafter routinely wax-embedded. An immunohistochemical technique, using a commercially available mouse monoclonal antibody to an ER-related antigen (Coffer *et al.* 1985), has been employed (D5, Amersham Laboratories), with an avidin-biotin method (Vector Laboratories Ltd, Cambridge, UK).

Results

Mean serum E2 levels achieved over a 28 day cycle of replacement therapy are displayed in Table 2. On days 1–5 of the cycle (equivalent to the very early proliferative phase) and days 15–19 (comparable to the early luteal phase) mean serum E2 levels in the study group were a little higher than in the control group, although in each situation the mean levels lay within the 95% confidence interval observed in the control group. Thus physiological levels of E2 were achieved with transdermal E2 delivery.

Figure 1 displays the mean (SE) serum progesterone levels attained with each mode of replacement regimen. Significantly higher levels were obtained after the two vaginal progesterone regimens ($P<0{\cdot}01$). Table 3 provides detail of the mean, SE and range of serum progesterone levels achieved with each regimen. The mean oestradiol/progesterone (E2/P) ratios in

Table 1. Clinical characteristics of the patients

Patient	Age (years)	Diagnosis	Time since last menstrual period
1	34	Idiopathic	15 months
2	37	Idiopathic	15 months
3	28	Idiopathic	18 months
4	28	Idiopathic	18 months
5	23	Idiopathic	36 months
6	33	Idiopathic	41 months
7	28	Idiopathic	5 years
8	32	Idiopathic	6 years
9	28	Idiopathic	11 years
10	23	Ovarian dysgenesis	Primary amenorrhoea
11	31	Ovarian dysgenesis	Primary amenorrhoea
12	36	Ovarian dysgenesis	Primary amenorrhoea
13	29	Ovarian dysgenesis	Primary amenorrhoea
14	30	Turner's syndrome	Primary amenorrhoea
15	30	Turner's mosaic	7 years
16	32	Post chemotherapy	9 years
17	34	Post chemotherapy	15 years
18	33	Surgical	7 years

the control group and the women receiving vaginal micronized progesterone were similar (8–15 pmol/nmol). Women using the vaginal pessary had a mean E2/P ratio similar to the control group only from day 19 onwards (12–13 pmol/nmol). In contrast the mean E2/P ratio for the women given oral micronized progesterone were 2–3 times greater than the control group ratios (37–44 pmol/nmol).

All endometrial biopsies conducted on day 10 or 11 after start of Estraderm revealed a proliferative endometrium. Similarly all biopsies taken after 3 days of vaginal progesterone replacement were considered physiological with expected 'third post-ovulatory day' features. In three of the four women investigated after 3 days of oral progesterone supplementation, histological appearances were physiological. The biopsy considered unphysiological displayed narrow, weakly secretory glands and a slightly pseudo-decidualized stroma. After 7 days of oral micronized progesterone supplementation the histological appearance was invariably of very abnormal appearance (Figure 2) with small inac-

Table 2. Serum oestradiol (E2) levels in patients and controls

Patients (n = 18)		Ovulating women (n = 60)	
Days of E2 replacement	Serum E2 (pmol/l)	Days from LH peak	Serum E2* (pmol/l)
1–5	295 (103–487)	−14	138 (81–222)
		−11	136 (64–253)
		−8	191 (103–327)
8–12	648 (260–1036)	−5	331 (155–625)
		−2	717 (309–1437)
		0	808 (236–2103)
15–19	609 (307–911)	+2	309 (139–599)
		+5	442 (178–935)
22–28	519 (357–681)	+8	507 (237–963)
		+11	438 (147–1030)
		+14	210 (67–505)

*Calculated as log values and back transformed.
Results are shown as means (95% confidence interval).

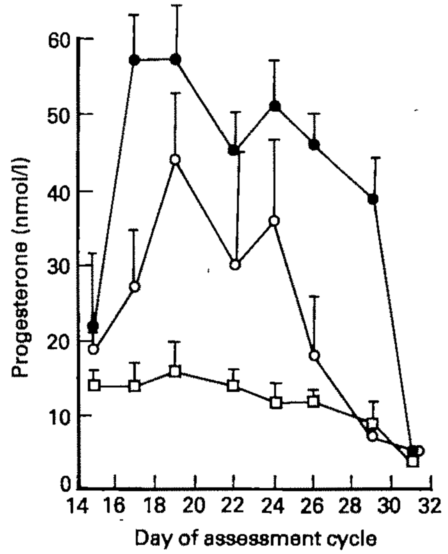

Fig. 1. Progesterone levels (mean + SE) during, (i) vaginal micronized (—●—, $n = 10$); (ii) vaginal pessary (—○—, $n = 4$) and (iii) oral progesterone replacement (—□—, $n = 10$).

tive glands set in a pseudodecidualized stroma and resembled the endometrium seen in certain combined steroid contraceptive users. Only one of the five women investigated had histological features that would be considered physiological on the 7 or 8th post-ovulatory day (Figure 3). In contrast such physiological features were observed in five of the six biopsies obtained after 7 days treatment with vaginal micronized progesterone; and in two of the four biopsies from women treated with vaginal progesterone pessaries. In the former group the one biopsy with an unphysiological appearance displayed narrow, exhausted secretory glands. In the latter group of endometrial samples, two biopsies contained narrow tubular glands and little secretory activity.

Immunohistochemical localization of the ER-Ag revealed that while on E2 replacement alone, immunostaining was localized to the cytoplasm of the glandular and luminal epithelium. There was no apparent nuclear staining and an absence of stromal staining (Figure 4). This was identical to the appearance seen in the late follicular phase of the normal cycle. After 3 days of progesterone supplementation (oral or vaginal) immunostaining persisted in the cytoplasm of the glands and lumen, but in addition stromal staining was expressed (Figure 5). Despite variable histology after 7 days progesterone replacement, a consistent immunostaining pattern was expressed. There was increased intensity of stromal cytoplasmic staining and a reduction in intensity of glandular staining regardless of the route of progesterone administration and the level of serum progesterone achieved.

Discussion

In this study we set out to examine whether normal endometrial appearances can be obtained by hormone replacement with transdermal oestradiol and progesterone, administered either orally or vaginally, later in the cycle. There are considerable advantages in using the natural steroids to support the endometrium in such women before ovum transplantation, not least of which is their ensured safety for the maintenance of pregnancy.

We found that we were able to achieve quite satisfactory and physiological E2 levels by applying transdermal oestradiol patches in increasing doses, up to a maximum of three Estraderm 50

Table 3. Serum progesterone (P) levels over 14 days of three regimens of progesterone replacement

	Serum progesterone concentration (nmol/l)								
	Vaginal micronized ($n = 10$)			Vaginal pessary ($n = 4$)			Oral micronized ($n = 10$)		
Day	Mean	(SE)	Range	Mean	(SE)	Range	Mean	(SE)	Range
15	22	10	3–61	19	3	7–12	14	2	11–18
17	57	9	31–99	27	8	9–44	14	3	7–30
19	57	11	27–128	44	9	20–59	16	3	10–29
22	45	5	26–69	30	16	12–61	14	2	7–26
24	51	6	23–76	36	11	14–63	12	2	6–17
26	46	4	25–63	18	8	10–34	12	1	9–14
29	39	7	17–71	7	2	5–9	9	4	3–19

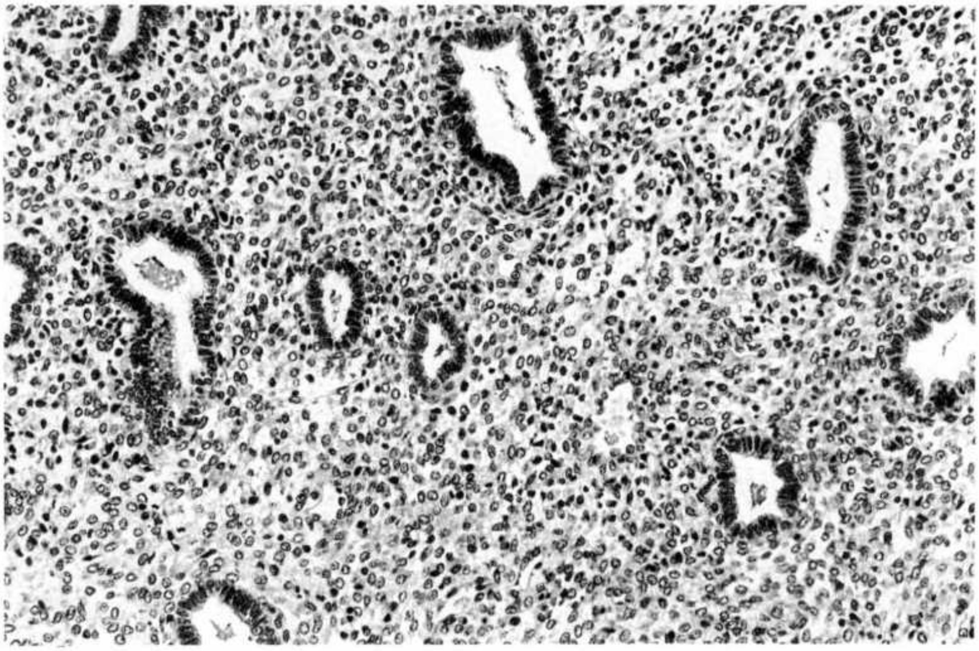

Fig. 2. Endometrial biopsy taken after 7 days of oral progesterone supplementation. The glands are narrow, tubular and almost totally inactive; the stroma is weakly pseudodecidualized. The appearances are similar to those seen in combined steroid contraceptive users. Haematoxylin and Eosin ×186.

patches. Overall mean oestradiol levels of 599 pmol/l after 8 to 26 days were achieved.

Regarding addition of progesterone, it is evident from our studies that dose for dose the vaginal is preferable to the oral route. Progesterone levels achieved by the latter were normal for the first 3 days, but thereafter stayed relatively low and did not achieve satisfactory mid luteal levels (mean 14 nmol/l). These low levels are reflected in the higher E2/P ratios seen with this route of progesterone administration. In contrast normal mid luteal levels were achieved with vaginal progesterone (mean 30 nmol/l with the pessaries, 100 mg/day, and 45 nmol/l with micronized progesterone, 300 mg/day).

It is appreciated that there is a wide range in progesterone concentration attained with these preparations when compared to the natural situation in which there is little variation. However, with the vaginal preparations despite these ranges in concentrations there was little variation in terms of the endometrial morphology.

The histological appearances of the endometrium were much as expected from these results. Normal proliferative phase features were observed during transdermal E2 supplementation, and the luteal phase endometrial appearance was judged overall to be adequate, with vaginal but not with oral progesterone. During vaginal administration not all samples were entirely physiological but only one woman failed to achieve normal features with micronized progesterone and two when using a vaginal pessary. The E2/P ratios observed with vaginal micronized progesterone closely resembled those in the control group, except in the instance where unphysiological endometrial morphology was noted and here the E2/P ratio (19 pmol/nmol) was a little higher than that of control group. In contrast with oral micronized progesterone only one woman demonstrated physiological features. The procedure of up to three serial endometrial biopsies in any one study cycle did not create a problem of morphological interpretation as biopsy of the same site was avoided by sampling from defined areas at each time period.

A further new feature of this study was the application of a monoclonal antibody to the 29 kilodalton protein (P29), which is not the E2 receptor itself but is related to it (Coffer *et al.* 1985). King & Coffer (1986) have indicated it is both qualitatively and quantitatively related specifically to the E2 receptor. Henry *et al.* (1988) reported use of the D5 antibody used in this study, to examine expression of the cytoplas-

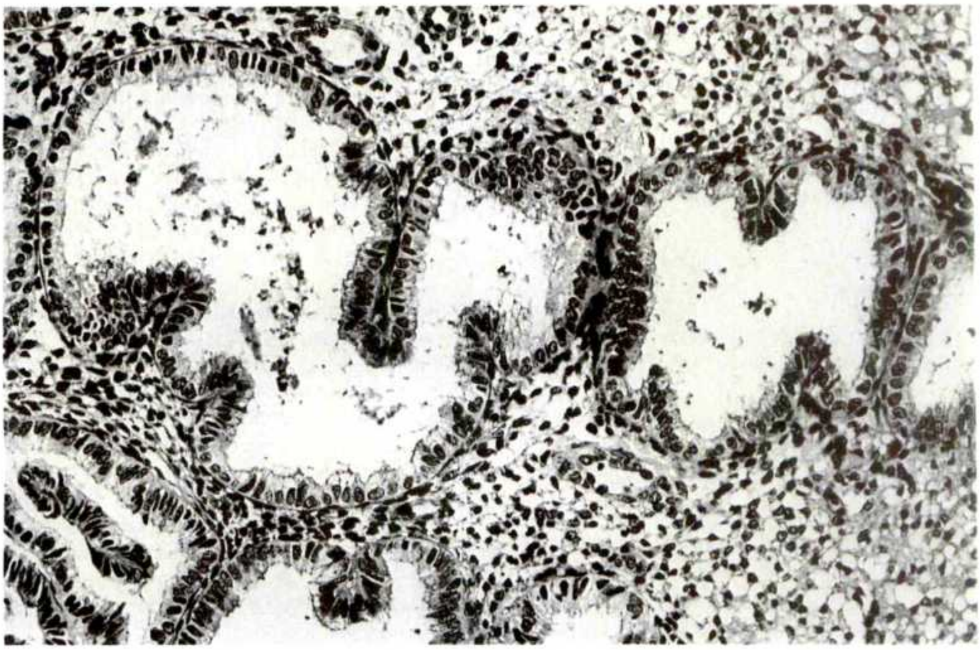

Fig. 3. Endometrial biopsy after 7 days of oral progesterone. The glands are well developed and mature and secretory activity is uniform and adequate. The appearances are indistinguishable from the 7th to 8th post ovulatory day. Haematoxylin and Eosin ×186.

mic oestradiol receptor in cervical tissue. To our knowledge there have been no reports using this antibody to study endometrial function in women with a premature menopause on steroid replacement therapy.

Our findings applying monoclonal antibodies directed at this receptor-related protein to normal endometrial tissue, and to endometrial tissue obtained from our treated woman were rather unexpected. Thus, as anticipated after a time on oestrogen alone, the protein was found to be expressed purely in the cytoplasm of the glands and surface epithelium. However, once progesterone was administered, the protein became manifest in the cytoplasm of stromal cells, and towards the end of the luteal phase the expression in the surface epithelium declined considerably. Evidently further studies are indicated to examine simultaneously the distribution of this protein and of oestradiol and progesterone receptors in the same cells, by applying

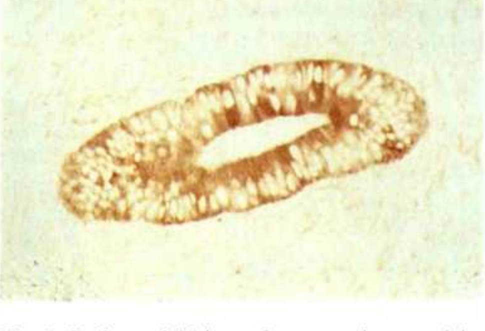

Fig. 4. Endometrial biopsy from a patient receiving only oestrogen. Oestrogen receptor related antigen is demonstrated in the glandular epithelium. Avidin-biotin immunohistochemical technique. Original magnification ×125.

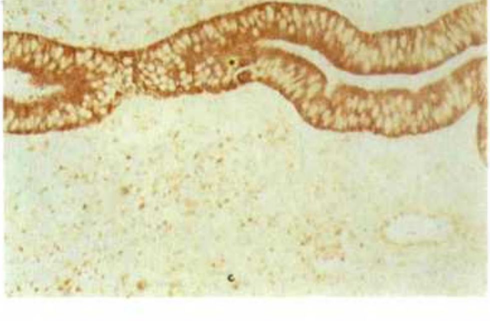

Fig. 5. Endometrial biopsy 3 days after vaginal progesterone. Oestrogen receptor related antigen is still present in the glandular epithelium but staining is also seen in the cytoplasm of the stromal cells. Avidin-biotin immunohistochemical technique. Original magnification ×100.

specific monoclonal antibodies to sequential sections. However, the fact that the normality of routine histological findings was supported by 'physiological' appearances applying a reagent which is evidently closely linked to oestrogen receptor action lends further support for this approach to the hormonal support of the endometrium in these women.

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Monoclonal antibody to ER-D5 antigen was supplied by Amersham Laboratories.

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Reliability of colposcopy and directed punch biopsy

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Summary. A group of 118 women underwent laser cone biopsy. Data were collected routinely on proforma case notes and entered into a computerized database. The histology of the cone biopsies was compared with that of previous, colposcopically directed punch biopsies, with the cytology of smears taken in the clinic and with the colposcopic diagnosis. The punch biopsy had a 54% false negative rate and neither of the two microinvasive carcinomas biopsied in this way were detected by the biopsy. Ten of 24 women with negative punch biopsies had CIN III in the cone. When the punch biopsy showed CIN II or worse, the cone biopsy confirmed the presence of CIN in 86%. There was some evidence of false negative cone biopsies. The data suggest that management should not be based solely upon the punch biopsy result but should include consideration of the cytology and colposcopy findings. Excisional methods of treatment are more likely to reveal early invasion and adenocarcinoma-in-situ.

Current practice in the management of women with abnormal smears is to base the decision to treat upon the result of a colposcopically directed punch biopsy unless the cervical cytology is severely abnormal. Several papers have reported the difficulty histopathologists face when reporting such biopsy specimens (Cocker *et al.* 1968; Ismail *et al.* 1989; Robertson *et al.* 1989). As a result it seems likely that women with invasive cancer may be being treated inadvertently by ablative techniques (Grundsell *et al.* 1983; Anderson 1986; Pearson *et al.* 1989) and that the treatment of many patients with CIN is being needlessly delayed (Bryne *et al.* 1988).

Dorsey and Diggs (1979) first described microsurgical conization of the cervix by carbon dioxide laser. This has been adapted for use under local anaesthesia in the out-patient clinic (Partington *et al.* 1987, 1989). The advantage of laser excisional cone biopsies over ablative techniques is the provision of a specimen for histological examination. This study compares the colposcopically directed punch biopsy diagnosis with the histology of the subsequent laser cone biopsy.

Patients and methods

Computerized data collection

From 1 November 1987, information obtained from all of the patients attending one of the colposcopy clinics at Hammersmith Hospital was recorded routinely on data sheets and stored on computer using a program written by one of the authors (WPS) in dBASE III Plus (Ashton Tate (UK) Ltd, Maidenhead) and compiled with Quicksilver (Wordtech Systems Inc, Orinda, California). The program was not created specifically for this project. It was designed to handle correspondence with patients and the referring

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doctors; to produce printed reports of the clinical and laboratory findings for the case notes; and to permit audit of all aspects of the work of the clinic. By the 28 February 1989, 118 of these patients had undergone a laser cone biopsy. These formed the basis of the study. The notes of a cohort of patients were examined to confirm the accuracy of the computer database.

Laser treatment—indications and technique

In this clinic, vaporization is normally only performed by inexperienced laser surgeons as part of their initial training and is confined to patients who, by all available criteria, have minor lesions. Laser excision is performed in over 75% of patients. Thus most of these laser cone biopsies were performed on women who would have satisfied the criteria for ablative therapy and all but 12 were performed under local anaesthesia in the out-patient department. However, five were done because of concern about the possibility of invasive disease; five because of abnormal glandular cells on the smear; ten because of previous treatment to the cervix; three because the whole lesion could not be adequately assessed colposcopically and three because of conflict between the colposcopic findings, the cytology result and the histology of the punch biopsy.

Apart from two women treated at the initial visit, the patients had a preliminary colposcopic assessment at which most had a cervical smear. A punch biopsy was taken only if the colposcopist believed that useful and reliable information could be obtained from the result. Thus, punch biopsies were not taken if part of the lesion could not be seen. At the second visit, using a NIIC 103 carbon dioxide laser (Sigmacon Ltd, Stanmore, Middlesex), a cone biopsy was excised, sometimes in combination with laser vaporization of the surrounding ectocervix if the lesion was extensive. The specimen was fixed in formalin and divided into blocks approximately 3 mm thick for histological examination. Two of these specimens were unsatisfactory for complete histological analysis.

Data analysis

For the purpose of this study the cytology, colposcopy and histology reports have each been categorized by the most severe abnormality seen. Wart virus changes, inflammatory changes and metaplasia have all been regarded as benign. If adenocarcinoma-in-situ (AIS) co-existed with a cervical intraepithelial neoplasm (CIN) the patient was classified by the former diagnosis. If AIS co-existed with squamous microinvasive carcinoma (MIC), the latter was regarded as the more significant lesion. Because AIS is not suitable for ablative therapy, it is considered together with MIC as 'early invasion'.

Results

Patients excluded from analysis

Three of the 118 patients were excluded from further analysis; one because of a long interval between the punch biopsy and the laser cone due to her not keeping her appointments, and two because the laser cone biopsy was unsuitable for full assessment.

Interval between assessment and cone biopsy

The mean interval between the initial assessment and the treatment visit was 10·1 weeks (SD 8·0, range 0–53). Of the six women with an assessment-treatment interval >24 weeks, the colposcopic findings were unchanged in four. In one, CIN I was seen on what had previously been regarded as a normal cervix. In the last, the colposcopic opinion of the lesion changed from CIN III to CIN II. In two women the delay in treatment was due to punch biopsies showing no abnormality or only trivial changes.

Punch biopsy

In 98 women a punch biopsy was taken. Of these, 92 were adequate for histological diagnosis and only 43 (47%) were said to show the same abnormality as seen subsequently in the cone biopsy specimen (Table 1). When the punch biopsy showed CIN II or worse, the cone biopsy confirmed the presence of CIN in 86%. Of the 24 women whose punch biopsies were said to show only benign changes, 13 (54%) had CIN in the cone biopsy specimen. Ten of these had CIN III. Nine of the 24 benign punch biopsies showed only wart virus change. CIN III was found in the cone biopsy from four of these nine women.

Detection of invasive disease by punch biopsy

Neither of the two women who proved to have

Table 1. A comparison of the histology of colposcopically directed punch biopsy with cone biopsy

	Cone biopsy						
Punch biopsy	Benign*	CIN I	CIN II	CIN III	MIC	AIS	Total
Benign	11	1	2	10			24
CIN I	6	2	2				10
CIN II	3	3	4	10			20
CIN III	5	1	4	25	2		37
MIC							0
AIS						1	1
Total	25	7	12	45	2	1	92

* Benign includes pure wart virus changes, metaplasia, inflammation and normal epithelium. CIN = cervical intraepithelial neoplasm; MIC = microinvasive carcinoma (squamous); AIS = adenocarcinoma-in-situ.

MIC, who had a punch biopsy taken, had their lesion detected by the initial biopsy. A punch biopsy correctly identified AIS in the only woman with this lesion who had a biopsy taken before treatment. Punch biopsies were not taken from the remaining two women with invasive cancer because the diagnosis was suspected from the colposcopic features in one woman with MIC and by severely abnormal glandular cells in the other who had AIS.

Cytology

A smear was taken from 104 women at their assessment visit. Four were unsatisfactory. Half of the women with negative smears or with mild dyskaryosis had CIN II–III (Table 2). Only 15% of the women with CIN III had a negative smear. Cytology suggested invasion in one of the two with MIC who had a smear taken at the assessment visit and the smear showed a glandular abnormality in both women with AIS. Of the five women with invasive disease, two were referred because of moderate dyskaryosis and in only one did the referral cytology suggest invasion.

False negative colposcopy

Colposcopy was unsatisfactory in three women (Table 3) Eight women with benign colposcopy were found to have disease in the cone biopsy; one with colposcopic evidence of metaplasia had CIN I in the cone biopsy; one had CIN III on an endocervical polyp and one had AIS.

This last patient and another with CIN II were the only patients with pathology in the cone biopsy in whom no abnormality of any sort was detected by the colposcopist. The clinician identified only wart virus changes in 6 of the 12 women with benign colposcopy but 4 of the 6 were found to have CIN in the cone biopsy, 3 having CIN III.

'False positive' colposcopy

The cone biopsy findings were negative in 24 women with colposcopic evidence of disease

Table 2. A comparison of the result of the smear taken at the first assessment with the histology of the cone biopsy

	Cone biopsy						
Cytology	Benign	CIN I	CIN II	CIN III	MIC	AIS	Total
Benign	5	3	3	6			17
Mild dyskaryosis	9	2	3	8			22
Moderate dyskaryosis	12	3	6	16			37
Severe dyskaryosis	3		3	13	1		20
Invasion					1		1
Abnormal glandular cells				1		2	3
Total	29	8	15	44	2	2	100

For abbreviations see Table 1.

Table 3. A comparison of colposcopy with the histology of the cone biopsy

	Cone biopsy						
Colposcopy	Benign	CIN I	CIN II	CIN III	MIC	AIS	Total
Benign	4	2	1	4		1	12
CIN I	4	3	3	5			15
CIN II	14	3	7	16	1	1	42
CIN III	6	1	6	27			40
MIC				1	1		2
AIS					1		1
Total	28	9	17	53	3	2	112

For abbreviations see Table 1

(Table 3). Twenty-three had punch biopsies taken and CIN was reported in 11 of these. All but one of the 11 also had an abnormal smear. Among the 13 women who had no punch biopsy taken or had a negative result, all but one had a dyskaryotic smear and one also had abnormal glandular cells.

Colposcopic and cytologic detection of invasion

One of the patients with AIS had no colposcopic abnormality at the first assessment. A cone biopsy was arranged because of the severity of the referral cytology. In the other woman with AIS, only the concomitant CIN III was recognized. One of the women with MIC was thought to have CIN II and the remaining two were identified at colposcopy (Table 3).

Of the five women whose laser cones were performed because of a suspicion of invasive disease, the ultimate diagnosis showed CIN III in two, MIC in two and AIS in one. Of the five done because of abnormal glandular cells in the smear, two had no abnormality, one had CIN III, one MIC and one AIS.

Discussion

Value of computerized audit

These data illustrate the value of computerized audit of colposcopy. The findings demonstrate what is actually happening in everyday clinical practice.

A disadvantage of this type of analysis is the possibility of a bias in the selection of patients. However, most of the women treated during this period underwent laser excision and no selection criteria were applied for laser excision which might affect the validity of the observations. It seems unlikely that the conclusions are prejudiced by unsuspected bias.

Correlation between punch biopsy and cone

The poor correlation between the colposcopically directed punch biopsy and the subsequent cone biopsy may be due to a sampling error in either biopsy. The colposcopist may not have selected the most severe part of the lesion or the pathologist may not have detected a small lesion in the cone biopsy (Burghardt 1981). Trauma to the biopsy, when it is being removed or during preparation in the laboratory, may remove abnormal surface epithelium. Further, considerable problems, especially with milder lesions, are inter-observer and intra-observer variation (Cocker *et al.* 1968; Ismail *et al.* 1989; Robertson *et al.* 1989).

The commonest disparity in this study was underestimation by the punch biopsy of the severity of the lesion. The false negative rate was 54%. Byrne *et al* (1988) found a 41·7% rate of false negative punch biopsy in their practice. It is of interest to note that, of 59 women attending this clinic who had negative punch biopsies during the same period and who were asked to return for further review, 13 (22%) were subsequently treated for CIN and 23 (39%) are still under observation.

These results are less encouraging than those reported by Kirkup *et al.* (1980). However, all of the biopsies in that study were examined by the same pathologist thus eliminating an important source of variation. In addition, only 8% of their patients had CIN I or less, the area where inter-observer variation is greatest. Results similar to the present study were reported by Holdt *et al.* (1982).

Invasive disease overlooked

There is considerable concern that early invasive lesions may be missed by colposcopically directed punch biopsy and then treated, perhaps inappropriately, by an ablative method (Grundsell *et al.* 1983; Anderson 1986; Pearson *et al.* 1989). Glandular abnormalities may also be overlooked. Burghardt and Holzer (1980), in a review of 1609 women with carcinoma-in-situ treated in Graz, reported higher rates of recurrence and of death among women in whom the diagnosis was based only upon a small biopsy. They concluded that this was due to inadequate diagnosis and a failure to detect invasive disease with punch biopsy. It is likely that cone biopsy will be superior to colposcopically directed biopsy because a greater volume of tissue is sampled and more sections are examined. However, false negative results may also occur in cone biopsy (Varga 1964), and observer variability will apply equally to the examination of cone biopsy and punch biopsy specimens.

Accuracy of colposcopy

The differences between the colposcopic diagnosis and the histology of the cone biopsy are disappointing. However, one of the eight 'false negative' colposcopies was a case of pure AIS—a lesion that cannot be detected reliably by this technique. Three women with CIN III were thought to have warty change only, a difficulty referred to by Walker *et al.* (1983) after finding CIN in 41·2% of women thought colposcopically to be pure viral infection. Many of the 'false positive' colposcopy results may in fact be false negative cone biopsies. This is suggested by the high prevalence of pathology reported in the punch biopsies and smears taken from these women and may be due to difficulties in handling some of the smaller laser cone biopsies in this series.

Conclusions

We conclude that the relatively poor agreement between the colposcopically directed biopsy and the cone biopsy suggests that management decisions should not be based solely upon the former but should include consideration of the cytology and the colposcopy. Treatment of cervical disease should consist of an excisional procedure to enhance the accuracy of the diagnosis although shortcomings in the diagnostic precision of cone biopsy must be recognised. The difficulty in identifying accurately 'pure' viral lesions or CIN I may explain in part the apparent progression of such lesions (Evans & Monaghan 1985; Campion *et al.* 1986), but suggests that it may not be wise to attempt to define with current techniques a group of such patients who do not require treatment and who can simply be observed.

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Prediction of pregnancy-induced hypertensive disorders by angiotensin II sensitivity and supine pressor test

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Summary. An angiotensin II sensitivity test and a supine pressor test were done consecutively at 28 weeks gestation in 90 healthy, normotensive nulliparous women. None of the supine pressor tests was positive, applying the predefined threshold of a rise of 20 mmHg in diastolic blood pressure after rolling over; nine tests were positive using a corrected 9 mmHg cut-off level. Ten women had a positive angiotensin sensitivity test using a threshold of the effective pressor dose of 8 ng/kg/min; 22 women were positive using an effective pressor dose of ≤10 ng/kg/min. Later in pregnancy 12 women (13%) developed pregnancy-induced hypertensive disease (PIH). The specificity of both tests of predicting the development of PIH was about 90%. The sensitivity of the angiotensin sensitivity test at the 10 ng/kg/min level was 92%. Because of its low sensitivity of 25% the supine pressor test appears to have no value for the prediction of PIH. There was a significant positive association between angiotensin II refractoriness and birthweight.

Various biochemical and biophysical tests have been devised for the prediction or early detection of pregnancy-induced hypertensive disorders. Most of these tests are of historical value only (Chesley 1978), but the angiotensin II (AII) sensitivity test and the supine pressor test are still performed in apparently healthy women in the late-second trimester of pregnancy to select individuals at risk for pregnancy-induced hypertensive disorders for preventive or therapeutic measures (Wallenburg *et al.* 1986; Spitz *et al.* 1988, Schiff *et al* 1989). Based on earlier observations that the physiologic refractoriness to the pressor response to angiotensin II in pregnancy is, to a large extent, lost in hypertensive pregnancy (Chesley 1966), both the AII sensitivity and pressor response tests were proposed by Gant *et al.* (1973, 1974). These investigators found each test highly reliable in predicting or excluding the subsequent development of pregnancy-induced hypertension (PIH). Since then, the supine pressor test has been assessed in many clinical studies covering more than 1500 pregnant women, with markedly disparate results (Wallenburg 1989). In contrast, a search of the literature revealed only four small studies which assessed the validity of the AII sensitivity test (Morris *et al.* 1978; Orozco *et al.* 1979; Oney & Kaulhausen 1982, Nakamura *et al.* 1986). The original study by Gant *et al.* (1973) has remained the only one published in the English literature in which the predictive values of each test performed in the same individuals were compared and were found to show excellent agreement.

Emerging possibilities of secondary prevention of pregnancy-induced hypertensive disorders (Wallenburg 1988) stress the need for a

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reliable and simple test for early identification of pregnant women with an elevated risk. We designed the prospective study to assess and compare the validity of the AII sensitivity and the supine pressor tests at 28 weeks' gestation in predicting or excluding the development of hypertensive disorders later in pregnancy.

Subjects and methods

Ninety healthy European nulliparous women attending the antenatal clinic of the Erasmus University Hospital Rotterdam were recruited for the study at 24–27 weeks gestation. The choice of sample size was based on our previous experience with the sensitivity test (Wallenburg *et al* 1986) in an attempt to collect 10–15 women who would develop a pregnancy-induced hypertensive disorder. The median age of the women was 24 (range 19–36) years, median weight 73 (range 47–92) kg. They used no medication except oral iron supplements, and diets were unrestricted. None of the women had a history of hypertension, cardiovascular or renal disease. Pregnancies had been uneventful with maximum diastolic blood pressures of 80 mmHg and adequate fetal growth. The study protocol was approved by the Hospital and University Ethics and Research Committee, and informed consent was obtained from all the women.

An AII sensitivity test was performed in each woman at 28 weeks gestation as recommended by Gant *et al.* (1973), in the left lateral recumbent position. An intravenous catheter was introduced into the right antecubital vein and connected to an infusion pump containing 50 μg of angiotensin-II-amide (Hypertensin, Ciba Geigy B.V., Arnhem, the Netherlands) in 50 ml of dextrose 5% solution. After insertion of the catheter, the woman rested on her left side for 15–20 minutes to stabilize the circulation. Blood pressure was then measured every 5 min on the left (inferior) upper arm using a mercury sphygmomanometer with a standard 12 cm wide cuff. The arm was placed in front of the subject with the cuff at the level of the heart. The auscultatory point of muffling of the Korotkoff sounds (phase IV) was recorded as the diastolic blood pressure. After a stable baseline diastolic pressure had been obtained during 15 min, the AII sensitivity test was done as described by Gant *et al.* (1973) Infusion of angiotensin II was begun at a rate of 3 ng/kg of body weight/min, and the dose was increased every 5 min by 1 ng/kg/min. The minimum amount of angiotensin II (ng/kg/min) that caused a rise of 20 mmHg over the baseline diastolic blood pressure was defined as the effective pressor dose. The test was stopped after the effective pressor dose had been determined in duplicate, or when infusion at a rate of 12 ng/kg/min had not yet caused a rise in diastolic blood pressure of 20 mmHg. An effective pressor dose of ⩽8 ng/kg/min was defined as a positive test according to Gant *et al.* (1973).

After infusion of angiotensin II had been discontinued the woman remained on her left side until her diastolic blood pressure had returned to its baseline level and had remained stable for 15 min. A supine pressor test was then done as described by Gant *et al.* (1974). The woman was instructed to turn from her left side onto her back and her blood pressure was measured immediately and again 5 min later; the highest diastolic blood pressure after turning supine was recorded. In 10 of the 90 women we did a supine pressor test before as well as after the AII sensitivity test, to assess a possible influence of the sensitivity test on the results of the following supine pressor test. A rise in diastolic blood pressure, after rolling over, of at least 20 mmHg over the baseline level was taken as a positive pressor response. This definition was derived from the original report by Gant *et al* (1974), which does not identify the arm used to record blood pressure. Since we used the left (inferior) arm, we corrected the 20 mmHg threshold for the predictable average hydrostatic increase in diastolic blood pressure of 11 mmHg that would have occurred after rolling-over if blood pressure had been taken from the right (superior) arm (Van Dongen *et al.* 1980), and we also assessed the significance of a diastolic pressure response of ⩾9 mmHg.

All tests were done by one investigator (J.W.M.). The results of the tests were not revealed to the women or to the attending obstetricians. All women received standard antenatal care in which the investigators were not involved. The clinical outcome of the pregnancies with respect to pregnancy-induced hypertensive disorders and birthweights was assessed from the charts after delivery. In this study PIH was defined as the occurrence before labour of a diastolic blood pressure (Korotkoff phase IV) of ⩾90 mmHg on at least two occasions ⩾4 h apart. PIH with proteinura of ⩾0·3 g in the absence of a urinary tract infection was defined as pre-eclampsia. Birthweight was expressed as birthweight index, that is the ratio of observed to expected birthweight according to the 50th centile of the distribution of birthweight corrected for gestational age and fetal sex (Kloosterman 1970).

Differences between diastolic blood pressure values obtained with the supine pressor test before and after the AII sensitivity test were statistically analysed with the rank-sign test. Correlations between measured variables of both tests, and between the results of both tests and birthweight indices were analyzed with the use of the Spearman test. A value of $P<0{\cdot}05$ was considered to represent significance.

Results

A stable diastolic blood pressure was obtained in all women, although it often took 20–30 min or more, in particular after angiotensin II infusion had been stopped. No significant difference was found between the results of the supine pressor test done before and after the AII sensitivity test in 10 women.

Since none of the 90 pregnant women investigated showed an increase in diastolic blood pressure of ≥20 mmHg after turning supine, all supine pressure tests were negative according to the original definition. Using the 9 mmHg level, nine women had a positive supine pressor test result (Table 1). The highest rise in diastolic blood pressure observed was 15 mmHg.

According to Gant's original definition 10 women had a positive AII sensitivity test result with an effective pressor dose of ≤8 ng/kg/min. Considering an effective pressor dose of ≤10 ng/kg/min to be a positive result (Oney & Kaulhausen 1982), 22 women were positive (Table 1). No correlation could be demonstrated between the effective pressor dose and the change in diastolic blood pressure after rolling over.

Subsequently three women developed PIH at between 39 and 41 weeks gestation and nine developed pre-eclampsia at a median gestational age of 38 (range 30–42) weeks; this gives a 13% prevalence of pregnancy-induced hypertensive disorders. None of the women became hypertensive in the immediate puerperium. The relation between the results of the two tests and the subsequent development of hypertensive disorders is presented in Table 1. The prognostic validity of both tests is summarized in Table 2.

We found a significant positive correlation between the effective pressor dose in the range of 5–12 ng/kg/min, and birthweight index (Fig. 1). Of the 22 women with an effective pressor dose of ≤10 ng/kg/min, nine gave birth to infants with a birthweight <10th centile of the reference curve (small-for-gestational age, SGA); four of these patients had pre-eclampsia. There were no SGA-infants in the group of the 68 women with an effective pressor dose of ≥11 ng/kg/min. None of the SGA infants had congenital abnormalities; all infants were born alive and survived.

Discussion

During their angiotensin II infusion studies, Gant *et al.* (1974) noted that many nulliparous, normotensive pregnant women who were sensitive to angiotensin II demonstrated an increase in diastolic blood pressure of ≥20 mmHg when they turned from their left side onto their back. Based on this post hoc observation the supine pressor or roll-over test came into being. The high sensitivity (88%) and specificity (95%) of this test reported by Gant *et al.* (1974) as a predictive test for pregnancy-induced hypertensive

Table 1. The development of pregnancy-induced hypertensive disorders related to the supine pressor (SPT) and the angiotensin II sensitivity test (AST) in 90 nulliparae at 28 weeks gestation.

	SPT Increase in DBP (mmHg)		AST EPD (ng/kg/min)		
Number of women	<9	≥9	5–8	9–10	≥11
Remaining normotensive	72	6	1	10	67
With pregnancy-induced hypertension	3	0	2	1	0
With pre-eclampsia	6	3	7	1	1

DBP diastolic blood pressure.
EPD effective pressor dose

Table 2. Sensitivity, specificity, and predictive values of the supine pressor test (SPT) and angiotensin II sensitivity test (AST) in 90 nulliparae at 28 weeks gestation.

	SPT ≥9 mmHg*	AST EPD (ng/kg/min)*	
		≤8	≤10
Sensitivity (%)	25	75	92
Specificity (%)	92	99	86
Predictive value of positive test (%)	33	90	50
Predictive value of negative test (%)	89	96	99

*Level defining a positive test.
EPD effective pressor dose.

disorders have not been confirmed in later studies. The various factors that may contribute to the marked disparity in reported results of this relatively simple test have recently been reviewed in detail (Wallenburg 1989). An important point is whether the left (inferior) or the right (superior) arm is used to record blood pressure when the woman is lying on her left side. Turning supine with blood pressure being measured on the left and inferior arm will cause little change in the vertical distance between the cuff and the level of the heart, and will therefore not cause an appreciable change in hydrostatic pressure. On the other hand, turning from the left side on the back with blood pressure taken on the right, superior, arm will result in a decrease of approximately 15 cm of vertical height between the cuff and the heart, and will thus cause a predictable hydrostatic rise in diastolic blood pressure of approximately 11 mmHg (Van Dongen *et al.* 1980). The original report of the supine pressor test as well as most later studies fail to identify the arm on which blood pressure was recorded; some authors state that they used the right, superior arm (Campbell 1978; Didolkar *et al.* 1979; Kuntz 1980). To prevent marked hydrostatic changes in blood pressure we used the left (inferior) arm to take blood pressure, which most likely explains the absence of an appreciable rise in diastolic blood pressure in most women after rolling over. Only nine women showed an increase in diastolic pressure of ≥9 mmHg which may be due to a 'pressor' effect other than that caused by hydrostatic factors. However, even using the 9 mmHg level to define a positive test, the sensitivity of the SPT remains too low to be of any clinical value.

The sensitivity and specificity of the AII sensitivity test determined in our study are comparable with the values that can be calculated from the original report by Gant *et al.* (1973). Our results are also in agreement with those reported by Öney & Kaulhausen (1982) in a group of healthy, pregnant European nulliparous women, with a prevalence of pregnancy-induced hypertensive disorders of 15%. In that study, using an effective pressor dose of ≤10 ng/kg/min to define a positive test, the sensitivity of the AII sensitivity test was 76%, and specificity was 83%. We prefer the threshold of 10 ng/kg/min to that of 8 ng/kg/min because the aim of the test is to detect more women at risk of developing PIH. Although use of this higher threshold increases the number of false positives, the specificity of 86% obtained in our study seems still acceptable. Results of studies in Asian (Nakamura *et al.* 1986) and South American (Orozco *et al.* 1979) women support the validity of the AII sensitivity test with a cut-off level of 10 ng/kg/min, although the numbers are small.

The significant positive association between angiotensin II refractoriness at 28 weeks gestation and birthweight index observed in our study has not been previously reported. This is a post hoc finding not related to a prespecified hypothesis, and as such it has limited value. It may serve, however, as a starting point for

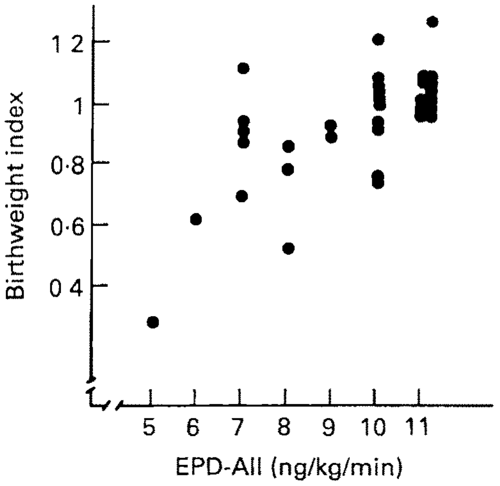

Fig. 1. Relation between effective pressor dose of angiotensin II (EPD-AII) and birthweight index in 34 nulliparous women with an EPD of ≤11 ng/kg/min ($P<0{\cdot}05$).

further investigations. There is evidence that the development and maintenance of an adequate uteroplacental circulation as well as the physiologic vasodilatation and blunting of the pressor response to angiotensin II in pregnancy depend on a dominance of the vasodilator effects of vascular prostacyclin over the vasoconstrictor effects of platelet thromboxane A_2 and other vasoconstrictor substances (Ylikorkala & Mäkilä 1985). Therefore, the observed relation between low birthweight and increased vascular responsiveness to AII could be explained by a prostacyclin-thromboxane A_2 imbalance in favour of thromboxane A_2, with an enhanced sensitivity to angiotensin as an early sign (Spitz *et al.* 1984).

In conclusion, in our hands the simple procedure of the supine pressor test at 28 weeks gestation has not proved useful for identification of pregnant women at risk for PIH. It seems likely that reported pressor responses to rolling over can be largely accounted for by hydrostatic changes. The AII sensitivity test has a good sensitivity and specificity but it is too complicated and time consuming to be used as a clinical screening procedure. The test may, however, be useful for research purposes to distinguish at 28 weeks gestation between women with a high risk of 40–50% and those with a low risk of 1-5% of developing pregnancy-induced hypertensive disorders, assuming a prevalence of 10-15%.

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The management of primary fallopian tube carcinoma

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Summary. The outcome of 30 patients with primary fallopian tube carcinoma is described. Treatment varied over the 22 year period of accrual and included combinations of surgery, radiotherapy and chemotherapy. There was an apparent increase in stage at treatment with time which was probably related to more precise staging at laparotomy and the greater use of computerized tomography. The median survival for all patients was 28 months and the 5-year survival was 18%. Ten patients received postoperative chemotherapy for residual disease with an overall response rate of 80% and median progression-free and overall survival times of 14 and 21 months respectively. The pattern of relapse was similar to that seen in ovarian carcinoma, with all but one patient having the pelvis or abdomen as the main site of recurrence. Primary fallopian tube carcinoma has a response to treatment and a tumour biology similar to that of ovarian carcinoma. It is recommended that the management of this uncommon malignancy should continue to be along the lines of ovarian carcinoma, with initial treatment by cytoreductive surgery followed by chemotherapy or radiotherapy for residual disease.

Primary fallopian tube carcinoma is an uncommon malignancy with a reported incidence between 0.3% and 1.6% of all gynaecological tumours (Raju *et al.* 1981). As a result of its rarity most reports from single institutions describe only a small number of patients and therefore it is difficult to analyse the survival rates of patients according to stage and initial treatment.

It has been usual in most centres to treat fallopian tube carcinoma in the same way as ovarian carcinoma. Surgery remains the mainstay of treatment and because ovarian malignancy is often suspected preoperatively, the surgical approach is similar. Subsequent therapy has varied but appears to have made use of those treatments available for ovarian carcinoma at the time of diagnosis and has usually involved pelvic or abdominal radiotherapy, single alkylating agent therapy or, more recently, platinum based combination chemotherapy.

This report summarizes experience in treating fallopian tube carcinoma at our institution over the past 22 years, and specifically examines whether the policy of treating this tumour in the same way as ovarian carcinoma is sound. Tumour extent at diagnosis, response to treatment, pattern of relapse and overall survival are examined and compared with the known clinico-pathological picture of ovarian cancer.

Subjects and methods

All primary fallopian tube carcinomas referred to this institution over the previous 22 years were identified from computer records and the medical records were examined. For all tumours, the pathology was reviewed by a panel of pathologists specializing in gynaecological tum-

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ours. Staging was based on the FIGO system for ovarian carcinoma and was undertaken retrospectively, based on the surgical and pathology records. The pattern of relapse was determined by the clinical findings noted in the records and by computed tomography (CT) and ultrasound scan results.

Results

Thirty tumours were identified and were available for assessment Only seven patients, with a median follow-up period of 10 months, remain alive. Others have died from fallopian tube carcinoma. The age of the patients ranged from 38–76 years with a median of 56 years. The most common presenting complaints were pelvic pain and abnormal vaginal bleeding. Of the 30 patients 24 had a total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSOH) at the initial operation, whereas six patients had a salpingo-oophorectomy alone. Postoperative treatment varied over the 22 years of the study, generally following that used for ovarian carcinoma at the time of diagnosis. Before 1980, 12 patients received radiotherapy postoperatively Radiotherapy was only used in those patients where residual tumour was suspected, either because this was noted at the time of surgery or because tumour rupture occurred during the operation. The radiotherapy treatment was consistent during this period, with fields confined to the pelvis in all patients. One patient also received intracavitary radium. No patient received whole abdominal fields as part of primary therapy. Doses ranging from 3000 to 4500 cGy with a median of 4250 cGy were given over 21 days in all patients.

The distribution of stage and treatment methods is shown in Table 1. Much emphasis cannot be placed on separate stages as earlier patients were probably understaged. There was an apparent increase in stage with time, related to the introduction of CT scanning, routine intra-operative staging biopsies and a change in the referral pattern. Before 1980, 14 of 18 (78%) patients were classified as stage I or II, compared with 2 of 9 patients (22%) after 1980. It is apparent, however, that tumour was invariably confined to the abdominal cavity at the time of diagnosis. Peritoneal, omental, mesenteric and local pelvic spread was common, whereas visceral involvement was confined to the liver (3 patients) and bladder (1 patient).

Table 1. Distribution of stage and primary treatment in 30 patients with fallopian tube carcinoma

Stage	Surgery	Surgery and radiotherapy	Surgery and chemotherapy	All treatments
I	3	2	0	5
II	3	7	2	12
III	0	2	8	10
IV	2	1	0	3

Response to treatment could be examined effectively only in the 10 patients who received postoperative chemotherapy. Patient characteristics, stage, response to treatment, progression free survival and overall survival are listed in Table 2. All patients had pre- and post-chemotherapy CT scans and four patients also had a second look laparotomy The overall response rate to chemotherapy was 80% with a median progression free survival of 14 months and median survival of 21 months.

The pattern of relapse, shown in Table 3, is very similar to ovarian cancer, with most patients showing relapse in the abdominal cavity, where the disease usually remained localized until death. Three patients developed malignant involvement of the supraclavicular fossa nodes but there was, in addition, extensive involvement of the abdomen and pelvis. One patient was unusual in that she developed a biopsy proven brain metastatis 31 months after a BSOH for stage Ia disease and then died from progressive cerebral involvement 15 months later, without clinical evidence of relapse elsewhere.

The median survival time for all assessable patients was 28 months and the 5-year survival rate was 18% (Figure 1). Survival according to stage or treatment must be interpreted with caution because of the probable understaging of patients during the initial decade of the study. The median survival time was 32 months for stage I, 25.5 months for stage II and 19 months for stage III and IV tumours. Patients treated with surgery alone survived for a median of 35 months and those treated with surgery and radiotherapy for 29 months. Patients treated with surgery and postoperative chemotherapy had a median survival time of 21 months. Three patients are alive, without evidence of disease, 2 years or more after treatment Two patients who were treated with BSOH followed by pelvic irradiation for stage IIb and III disease have no evidence of relapse after 5 years. A further

Table 2. Response to chemotherapy in 10 patients with fallopian tube carcinoma

Age (years)	Stage	Chemotherapy	Residual disease	Response	Progression free (months)	Overall survival (months)
60	III	Melphalan	>2cm	CR	8	27
64	III	Cyclo, cisplatin	>2cm	PR	10	12
41	III	Ifos, melphalan	>2cm	PD	2	8
59	III	CHIP	>2cm	PR	9	22
38	III	CHIP	>2cm	PR	17	21
44	IIb	Ifos, adria cyclo, carboplatin	>2cm	CR*	12+	12+
59	IIa	Ifos, adria cyclo, carboplatin	>2cm	PR*	33+	33+
48	III	Ifos, adria cyclo, carboplatin	>2cm	PR	6+	6+
50	III	Ifos, adria cyclo, carboplatin	<2cm	CR*	6+	6+
61	III	Ifos, adria cyclo, carboplatin	<2cm	SD*	7+	7+

*=pathological restaging at second look laparotomy, adria=adriamycin, ifos=ifosfamide, cyclo=cyclophosphamide, CHIP=cis-dichloro-transdihydroxy-bis-isopropylamine platinum IV, CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease.

patient received platinum containing combination chemotherapy after a BSOH for a stage IIa fallopian tube carcinoma and is alive with no evidence of relapse 33 months after the start of treatment.

Discussion

Previously reported series have emphasized the poor prognosis for patients with primary fallopian tube carcinoma with a 5-year survival rate of less than 20%, regardless of stage at diagnosis (Eddy *et al.* 1984a, Harrison *et al.* 1989). Residual tumour after surgical resection appears to influence survival Those with no visible residual tumour have a 5-year survival rate of 29% compared with less than 10% for those with macroscopic residual tumour (Eddy *et al.* 1984a).

Table 3. Pattern of relapse in patients with fallopian tube carcinoma

Site of relapse	Number of patients
Pelvis	4
Pelvis+peritoneum/omentum	9
Pelvis+peritoneum/omentum+wound scar	3
Pelvis+peritoneum/omentum+SCF	3
Pelvis+peritoneum/omentum+liver	2
Pelvis+peritoneum/omentum+pleural effusion	1
Brain	1

Many investigators have attempted to produce survival rates for various different treatment regimens. This may give a false impression of relative merits because of difficulty interpreting the results obtained from different decades of a study period. In the largest series reported, 71 patients were available over a 33 year period,

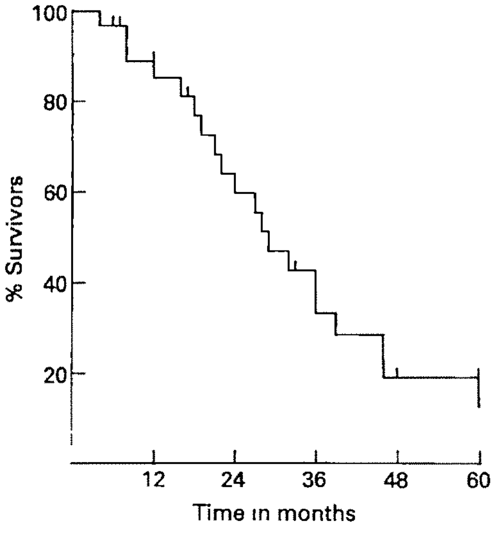

Fig. 1. Overall survival of 30 patients with primary fallopian tube carcinoma.

giving an average accrual rate of less than three patients per year (Eddy *et al.* 1984a) and most reports from other centres have had a similarly slow rate of accrual. Staging procedures and treatment patterns changed dramatically over that period, therefore any comparison of these therapies must be interpreted with caution. As demonstrated in our study, an apparent increase in incidence of stage III and IV disease occurs with time, as more effective staging procedures are instigated Modern surgical techniques potentially allow for greater initial clearance of tumour, which adds to the difficulty of comparing the effectiveness of present day platinum based adjuvant treatment with that of earlier adjuvant therapy This may partially explain the absence of a statistically significant difference between treatment groups in this and other studies (Eddy *et al.* 1984a, Harrison *et al.* 1989).

Comparison of fallopian tube malignancy with ovarian carcinoma has been made previously (Dodson *et al.* 1970). Both tumours arise in tissue derived from the Mullerian tract. There are also many histological similarities between the two tumours (Talamo *et al.* 1982) We have demonstrated that the tumour biology, in respect to both the route of spread and host survival, is almost identical. Other series have also drawn attention to the pattern of spread and the propensity for recurrence of the tumour in the abdominal cavity (McMurray *et al* 1986, Denham *et al.* 1984). Extra-peritoneal metastases have been recorded in fallopian tube carcinoma but they generally occur in association with extensive intraperitoneal recurrence (Yoonessi *et al.* 1979). This tumour has consistently been shown to be chemosensitive (Boronow 1973, Deppe *et al* 1980). A high response rate to cytotoxics has been confirmed in two reports on the results of second look laparotomies after adjuvant therapy. Pathologically confirmed complete response rates up to 50% were demonstrated in patients treated with melphalan and hormonal therapy for residual disease after BSOH (Eddy *et al.* 1984b) and Jacobs *et al.* (1986) demonstrated a similar response rate with platinum-based chemotherapy.

The rarity of primary fallopian tube carcinoma constitutes a problem in determining the most effective treatment available. The low accrual rate in any single institution makes it difficult to examine different methods of treatment prospectively. Retrospective analysis poses problems with comparability, already outlined; it is also unusual for a standard treatment to have been maintained over a long period. In view of the similarities between primary fallopian tube and ovarian carcinoma in terms of tumour biology and reponse to treatment, it would be reasonable to treat this uncommon tumour with treatment programmes similar to those currently used for ovarian carcinoma.

It may be unrealistic to recommend a multicentre trial of treatment for this malignancy, since the amount of useful information obtained is likely to be small in relation to the cost. Even with ovarian carcinoma, a much more common tumour, trials have resulted in no standard or clearly superior treatment regimen. This is despite the study of large numbers of patients receiving various innovative combinations of chemotherapy, radiotherapy and surgery. More effort should be directed at defining the biology of fallopian tube carcinoma in autopsy series; increased use of second look laparotomy after adjuvant therapy may also help in this regard Until more information is available, the current evidence suggests that primary fallopian tube carcinoma should continue to be treated along the lines of ovarian carcinoma with initial treatment by cytoreductive surgery followed by chemotherapy or radiotherapy for residual disease.

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Prostaglandin induced cervical ripening under tocolytic cover in primiparae: results of a double blind placebo controlled trial

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Summary. In a double blind trial, 60 nulliparae with a modified Bishop score of ≤5 requiring induction of labour, received either 8 mg of salbutamol or an identical placebo orally, 30 min before vaginal administration of 2 mg prostaglandin E_2 gel. Women in the salbutamol group experienced less uterine activity over the subsequent 12 h compared with those given placebo, and fewer (35%) commenced labour compared with the placebo group (62%). However, the change in cervical score was significantly less in the salbutamol group (mean 3·0, SD 3·1) than that in the placebo group (mean 5·8, SD 3·2), and the prostaglandin treatment to delivery time in the salbutamol group (mean 26·1 h, SD 6·49) was significantly longer than that in the placebo group (mean 19·3 h, SD 7·95). The first stage of labour lasted >10 h in 11 women in the salbutamol group compared with five in the placebo group. Side effects attributable to salbutamol occurred in 10% of the treated women but in none of their fetuses and fetal outcome was satisfactory and similar in both groups. Our findings show that salbutamol can suppress prostaglandin-induced uterine activity during cervical ripening, which could be an advantage in induction of labour where a planned delivery is preferred. However, the poorer outcome of labour in salbutamol-treated women mitigates against this approach.

The benefits of vaginal administration of prostaglandins for cervical ripening before induction of labour are well recognized. The optimum time for the prostaglandin to promote cervical ripening is variable and may take >12 h (Walker & Gordon 1983). A proportion of the women treated with vaginal prostaglandins will go into labour during that time, when the delivery unit may not have adequate resources to monitor the labour or to care for a distressed or immature infant.

It has been shown that oral administration of tocolytics before vaginal prostaglandins appears to suppress both prostaglandin-induced uterine contractions (Goeschen *et al.* 1985), and the onset of labour (Insull *et al* 1989), while allowing cervical ripening to take place. The outcome of labour did not appear to be adversely influenced in either study, indicating that this approach to labour induction may have advantages where placental insufficiency is suspected.

To explore this concept objectively, a double blind placebo controlled study was conducted in primiparae with an unripe cervix requiring labour induction, to determine the effects upon

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cervical ripening, labour progress, and neonatal outcome

Subjects and methods

Sixty nulliparae with a singleton fetus and cephalic presentation booked for induction of labour because of hypertension or prolonged pregnancy, and without evidence of placental insufficiency, were recruited after approval from the ethics committee.

The women were entered into the trial on the evening before planned induction. The cervix was assessed and if the Bishop score was <6, baseline observations of blood pressure, temperature and pulse were made. A blood sample was collected from a vein in the antecubital fossa for salbutamol analysis, and external cardiotocography was started. Each woman was then randomly allocated to receive either 8 mg of salbutamol (Ventolin Spandets: Allen & Hanburys) or identical placebo orally according to a predetermined code kept in the pharmacy and not broken until completion of the study. Thirty minutes later 2 mg of prostaglandin E_2 (PGE_2) gel (Prostin E_2 vaginal gel: Upjohn) was instilled into the posterior vaginal fornix. Maternal pulse rate was recorded at 30 min intervals for a further 90 min, at which time cardiotocography was discontinued, and a further blood sample taken for salbutamol analysis. In all women any symptoms attributable to salbutamol, and the occurrence of contractions, or established labour overnight were recorded.

Approximately 14 h later, the same clinician assessed the cervical state again without reference to the previous cervical score in those women who had not begun labour overnight. When the cervix was sufficiently dilatated, the women had a low amniotomy and a titrated infusion of oxytocin was started 1 h later at 2 mu/min increasing to a maximum of 48 mu/min as necessary to establish labour. Where amniotomy was not possible, further treatment with either prostaglandin or a titrated infusion of oxytocin was started, and amniotomy performed when cervical dilatation was adequate.

Subsequent management of labour was by the duty delivery suite staff. At birth, umbilical artery and vein blood gas analyses were performed; in addition a blood sample was collected from the umbilical vein, and a further maternal blood sample was obtained for measurement of salbutamol concentration. Salbutamol was estimated by solid phase extraction and high performance liquid chromatography (Pickup & Harrison 1987).

Results

Patient details relating to age, height, weight, gestation, and Bishop score before treatment are shown in Table 1. There were no statistically significant differences between the two groups (Student's *t*-test).

The effects of salbutamol are shown in Table 2 The mean number of contractions recorded over a 10 min period on the tocograph before treatment and 2 h after treatment were not significantly different in either the salbutamol or the placebo group. However, uterine contractions were experienced during the night by 20 (64%) women in the salbutamol group, compared with 26 (90%) in the placebo group ($P < 0{\cdot}05$; χ^2-test). Eleven (35%) women treated with salbutamol started labour overnight compared with 18 (62%) treated with placebo ($0{\cdot}1 > P > 0{\cdot}5$). Headache or vomiting was experienced by 10% of the women treated with salbutamol compared with none treated with placebo.

The mean change in cervical score in the salbutamol treated women was 3·0 (SD 3·1) com-

Table 1. Characteristics of the women in the study

	Salbutamol ($n = 31$)	Placebo ($n = 29$)
Age (years)	24·5 (4·8)	25·3 (4·6)
Gestation (weeks)	40·9 (1·0)	40·7 (1·2)
Maternal weight (kg)	77·6 (10·7)	80·1 (10·1)
height (m)	1·6 (0·05)	1·6 (0·1)
No. of women with pre-treatment Bishop scores		
1–2	8	5
3–5	23	24

Results are mean (SD) values.

Table 2. Effects of salbutamol during cervical ripening

	Salbutamol (n = 31)	Placebo (n = 29)
No of contractions/10 min on cardiotocograph		
Before salbumatol	1·2 (1·1)	1·3 (1·1)
2 h after salbutamol	2·7 (1·2)	3·0 (1·5)
No of women with contractions overnight	20 (64%)	26 (90%)
No of women with onset of labour overnight	11 (35%)	18 (62%)
No. requiring more oxytocin before amniotomy	9 (23%)	2 (7%)
Change in Bishop score		
All women	3·0 (3·1)	5·8 (3·2)
Women without onset of labour	1·5 (1·7)	2·9 (1·6)

Results are means (SD) or n (%) as appropriate

pared with 5·8 (SD 3·2) in the placebo treated women ($P < 0·05$ Student's t-test). Considering only those women who had not started labour, the change in cervical score was also significantly less in the salbutamol group (mean 1·5, SD 1·7, $n = 20$), compared with the placebo group (mean 2·9, SD 1·6; $n = 11$) ($P < 0·05$). In nine women treated with salbutamol the change in cervical score was ≤ 1 and they required further treatment before induction of labour, compared with only two in the placebo group ($0·1 > P > 0·05$; χ^2-test).

In the salbutamol group, the mean maternal plasma salbutamol concentration was 4·74 ng/ml (SD 3·58) 2 h after treatment and 1·49 ng/ml (SD 1·48) after delivery, whilst the umbilical vein concentration at delivery was 1·55 ng/ml (SD 1·26).

Table 3. Outcome of labour in the study groups

	Salbutamol (n = 31)	Placebo (n = 29)
Prostaglandin-to-delivery interval* (h)		
All women	26·1 (6·49)	19·3 (7·95)
Women without onset of labour overnight	29·0 (4·8)	25·4 (5·2)
First stage (h)	8·2 (3·8)	7·5 (4·1)
First stage > 10 h	11	5
Maximum rate of oxytocin (mu/min)	24·6 (11·0) (n = 18)	22·4 (15·8) (n = 15)
Mode of delivery		
Spontaneous	16 (51%)	16 (55%)
Forceps	12 (39%)	10 (35%)
Section	3 (10%)	3 (10%)
Umbilical blood pH		
Artery	7·21 (1·0)	7·19 (0·8)
Vein	7·31 (0·7)	7·29 (0·8)
Birthweight (g)	3477 (436)	3329 (746)
Apgar score at 1 min		
1– 4	3	1
5– 7	3	5
8–10	25	23
Apgar score at 5 min		
1– 4	0	0
5– 7	1	0
8–10	30	29

*Three women (one in the salbutamol and two in the placebo group) who were not induced the next day are excluded from this analysis (see text)
Results are means (SD) or n (%) as appropriate

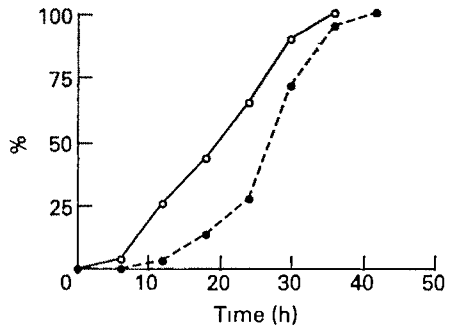

Fig. 1. The cumulative percentage of deliveries with time after vaginal prostaglandin administration ——○—— women treated with placebo, ---●--- women treated with salbutamol

There was no association between salbutamol levels and side effects from salbutamol, or the occurrence of contractions, pain or establishing labour during the night. Salbutamol was not detected in any of the plasma samples in the placebo group.

The outcome of labour and neonatal condition are shown in Table 3. The mean prostaglandin-to-delivery interval in the salbutamol group was 26·1 h (SD 6·49), this was significantly longer than that in the placebo group (mean 19·3 h, SD 7·95) (P <0·05 Student's t-test). The cumulative percentage of deliveries by time after PGE_2 administration are shown in Fig. 1 for the two groups. The first stage of labour was > 10 h in 11 women treated with salbutamol compared with five women receiving placebo (0·2 > P >0·1; χ^2-test); 20 women (65%) in the salbutamol group required epidural analgesia compared with 11 (39%) in the placebo group (0·1 > P >0·05). Three women in each group were delivered by caesarean section· two for failure to progress and one for fetal distress in the salbutamol group; one for failure to progress and two for fetal distress in the placebo group There was a retained placenta in one woman treated with salbutamol, and three women in each group sustained an estimated blood loss of 500–1000 ml during or immediately following the third stage of labour. one placebo treated woman had an inverted uterus in the third stage of labour with 2000 ml blood loss, the uterus was repositioned and she was transfused.

Induction of labour was not possible the next day in three women, but all were later induced successfully. One of these women who had received salbutamol was delivered by caesarean section for fetal distress after 5 h in the first stage of labour, whereas the other two, both in the placebo group, gave birth spontaneously.

There were no neonatal complications before discharge in any of the women in the study. All the newborn infants had 5-min Apgar scores of ⩾8 except one baby in the salbutamol group. Thick meconium was noted at the birth of this baby who was immediately intubated to ensure the upper airway was cleared and the 10-min Apgar score was 9.

Discussion

Tocolytic cover with oral salbutamol almost halved the proportion of women who went into labour after vaginal PGE_2 compared with the placebo group.

We reported previously the occurrence of labour in an uncontrolled study of oral tocolysis at 19% in a similar group of women: in that study the prostaglandin was given as a vaginal pessary rather than viscous gel, and this may have influenced the release of prostaglandin. The mechanism of action of salbutamol is probably through interference with intracellular calcium channels thereby both reducing prostaglandin-induced myometrial contractility (Huzar and Naftolin 1984, Garfield 1984), and adversely influencing endogenous prostaglandin synthesis (Gorraci *et al.* 1978). The rate of onset of labour during the ripening process in the placebo group was similar to that reported previously for primiparae with Bishop scores of ⩽5 (MacKenzie and Embrey 1978, Shepherd *et al* 1981).

Salbutamol treatment appears to inhibit prostaglandin-induced uterine contractions at the expense of cervical ripening, suggesting the importance of myometrial contractility in cervical ripening. These results are at variance to the findings of Goeschen *et al.* (1985) who found that oral tocolytics given 30 min before PGE_2 application in 17 women with an unripe cervix (Bishop score ⩽6) successfully suppressed prostaglandin-induced uterine contractions without affecting cervical ripening compared with 17 controls. The differences might be explained by the fact that their observations were based on cervical assessment 8 h after prostaglandin administration in women of mixed parity, some of whom had prelabour rupture of membranes.

Although prostaglandin-induced uterine contractions may be acutely suppressed by tocolytics (Maclean and MacKenzie 1980), effective sustained tocolysis was not achieved in a substantial minority in this study. Further suppression of contractility would be necessary if the onset of labour was to be prevented. This might be possible with a larger or repeated tocolytic dose: plasma levels of 8–33 ng/ml are necessary to inhibit uterine contractions in preterm labour (Hutchings *et al.* 1987), but this concentration was achieved in only four women, one of whom still laboured during the night. However, the poorer outcome of labour in salbutamol treated patients mitigates against this approach, and the possibility of an increased risk of post-partum haemorrhage following additional betamimetic inhibition of myometrial activity must be considered, although there was no evidence of this in the present study. Intravenous or intramuscular salbutamol is unlikely to convey any advantage, but local administration might be worth exploring, perhaps as a combined preparation.

By reducing the occurrence of labour overnight, salbutamol prolongs the prostaglandin-to-delivery time, which in general might not be considered an attractive development by women or staff. Nevertheless, in pregnancies with suspected placental insufficiency, or where a need for intensive neonatal care immediately after delivery is anticipated, as with major structural abnormalities or severe rhesus incompatibility, there are potential benefits in postponing labour to a time when delivery suite and neonatal unit staffing levels are able to provide optimum conditions. However, as discussed above there are other disadvantages to this approach.

An alternative to this approach is the cross-linked hydrogel polymer pessary providing sustained constant release of prostaglandin demonstrated both *in vitro* (Embrey *et al.* 1986) and *in vivo* (MacKenzie *et al.* 1988). This has been shown to effectively ripen the unfavourable cervix and induce labour in more favourable conditions. Its release profile may allow cervical ripening to take place without further compromising a high risk pregnancy, and this concept requires more attention.

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The rate of rise of corticotrophin releasing factor and endogenous digoxin-like immunoreactivity in normal and abnormal pregnancy

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Summary. Maternal plasma concentrations of corticotrophin releasing factor (CRF) and endogenous digoxin-like immunoreactivity (EDLI) were estimated in 80 normal and 88 abnormal pregnancies which were sampled sequentially from 24 weeks gestation to delivery. A slope was fitted for each woman's antenatal EDLI and CRF values, both of which rose significantly during gestation, and the mean of the slopes for the normal and abnormal groups for each value compared. There was no evidence of significant mean differences between groups for EDLI but there was evidence of a significant mean difference for CRF ($P<0 \cdot 05$). After adjustment for other variables which may affect pregnancy outcome, the slopes for CRF were found not to be significantly related to outcome.

Corticotrophin releasing factor (CRF) is a peptide produced in the hypothalamus which is released in response to stress to stimulate pituitary corticotroph activity. Plasma levels of CRF are low or undetectable in the normal non-pregnant woman (Linton *et al.* 1987; Cunnah *et al.* 1987) but are measurable in normal pregnant women in the third trimester. The higher levels of CRF detected in maternal plasma in the third trimester are placental in origin, CRF-like immunoreactivity and bioactivity having been identified in extracts of human term placentas (Shibasaki *et al.* 1982; Sasaki *et al.* 1984; Wolfe *et al.* 1988; Goland *et al.* 1987) and HPLC showing maternal plasma CRF to be chromatographically indistinguishable from synthetic CRF. The CRF gene is expressed in the human placenta (Grino *et al.* 1987). Placental CRF mRNA has been reported to be located in the syncytiotrophoblast (Frim *et al.* 1987). In a previous cross-sectional study we reported significantly elevated CRF levels in pregnancy-induced hypertension (PIH) and preterm labour (Wolfe *et al.* 1988) but the reason for these findings is unclear and the observations were not based on a prospective study.

Maternal serum in the third trimester (Graves

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et al. 1984; Koren *et al* 1984) and neonatal serum (Koren *et al.* 1984; Valdes *et al.* 1983; Morris *et al.* 1987) demonstrate 'false positive' results with a number of different radioimmunoassays for digoxin. The presence of this endogenous digoxin-like immunoreactivity (EDLI) therefore hinders the clinical estimation of digoxin. Most EDLI has been attributed to high serum concentrations of progesterone, cortisol and dehydroepiandrosterone sulphate (DHA-S) all of which have been found to bind non-specifically to digoxin (Logerich *et al.* 1988). However, EDLI is also associated with true digoxin-like activity (Morris *et al.* 1987). The high values of EDLI in fetal compared with maternal serum (Koren *et al.* 1984; Morris *et al.* 1987), a correlation between fetal and maternal EDLI (Koren *et al.* 1984), and the rapid disappearance of EDLI from maternal serum postpartum (Witherspoon *et al.* 1986) lend support to the theory that EDLI originates in the fetoplacental unit.

Abnormally high values of EDLI in maternal plasma have been reported in some (Gusdon *et al.* 1984; Graves *et al.* 1984) but not all (Phelps *et al* 1988) studies of gestational hypertension. EDLI is also very high in infants born preterm (Koren *et al.* 1984; Morris *et al.* 1987). High EDLI in the serum is also associated with renal failure and with liver disease (Witherspoon *et al.* 1986). To date, no study has attempted a sequential estimation of EDLI throughout the third trimester

The possibility that raised levels of either CRF or EDLI are present before abnormal pregnancy states and are able to predict abnormal pregnancy needs to be addressed. This prospective study set out to describe the sequential changes in maternal plasma levels of both EDLI and CRF in normal and abnormal pregnancies.

Subjects and methods

The study involved 168 pregnant women who had venous plasma samples taken at 2-4 weekly intervals to estimate CRF and EDLI concentrations from 24 weeks until delivery. Eighty women had a normal pregnancy which was defined as a spontaneous vaginal delivery at term (>37 weeks) of a baby weighing >2·5 kg. For each estimation, 10ml of venous blood was collected in a heparinized tube and kept on ice until centrifugation at 4°C for 10 min. Aliquots of 1ml were snap frozen on solid CO_2 and stored at −80°C until assay.

The other 88 women comprised a heterogenous group of abnormal pregnancy states Some of them were chosen at random as being at high risk for certain abnormalities because they had had an abnormal pregnancy previously with either pregnancy-induced hypertension (PIH), antepartum haemorrhage or a small for gestational age (SGA) fetus. Fifteen women had a preterm labour (<37 completed weeks), 16 women had an antepartum haemorrhage (APH) (abruption or placenta praevia), 16 gave birth to SGA infants (<2·5 kg at term), 20 sufferd from PIH (blood pressure >140/90mmHg on two occasions with or without significant proteinuria) with no history of essential or chronic hypertension and four were diabetic. The remainder were classified as abnormal because the mode of delivery was by caesarean section or by forceps for fetal distress.

CRF was measured directly in 200 μl of plasma using a two-site immunoradiometric assay (IRMA) (Linton *et al.* 1987). The sensitivity of the IRMA is 1 pg/ml. EDLI was measured in one batch using a test kit for RIA determination of serum digoxin with the RIANEN (NEAC82 double antibody assay) assay (New England Nuclear-Dupont, Wilmington, DE, USA). This assay uses a rabbit digoxin antibody prereacted with an antiserum to rabbit gamma globulin The limit of detection of the assay was determined as 0·06 nmol digoxin/l. No patients had chronic hypertension, acute or chronic renal dysfunction, or liver dysfunction which are known to cause elevation of EDLI independent of pregnancy.

Details of the patients' age, race, past obstetric history, blood group, sickle status, smoking habit, weight gain in pregnancy and maternal weight were recorded along with details of gestational age at the time of onset of labour, whether labour was spontaneous or induced and the length of the first stage, fetal sex, weight and placental weight. Gestational age was calculated using the 16-week ultrasound biparietal estimation.

The median values of EDLI and CRF measurements for both normal and abnormal groups at each gestational age were calculated from 24 weeks. A regression coefficient on time was fitted to each woman's antenatal CRF and EDLI values from 24 weeks to describe their rate of increase on a weekly basis and the means of the slopes for the normal and abnormal groups were compared using the unpaired *t*-test.

A logistic regression model with the dependent variable being an outcome of normal or abnormal was constructed to adjust for those variables which may affect outcome. These variables were age, race, previous PIH, placental weight, smoking, gestation, number of previous pregnancies. An abnormal outcome included all pregnancies in which a normal pregnancy without antenatal complications and with spontaneous vaginal delivery at 37 completed weeks of a baby weighing >2·5 kg did not occur. Analysis was carried out using the statistical program GLIM (Baker *et al.* 1987).

Results

CRF measurements were not normally distributed, but were approximately normal after $\log_e$ transformation. Logistic regression analyses were performed on log transformed values. The distribution of the means, SDs and median values for CRF is described in Table 1. Because of zero values, EDLI measurements could not be log transformed and were not normally distributed. Table 2 describes the distribution of the mean, SD and median values for EDLI. Both CRF and EDLI values increased significantly with gestational age ($P<0·01$) when a straight line was fitted for each subjects values.

A slope was fitted to interpret the average change per week of gestation for each subject in the normal and abnormal groups for the variables EDLI and $\log_e$ CRF. The mean of the slopes in each group were compared using the unpaired *t*-test. The mean of slopes for EDLI were: normal ($n=79$) mean slope 0·013 (SD 0·007); abnormal ($n=87$) mean slope 0·014 (SD 0·014) and the difference was not significant ($P=0·4$) (95% CI for the mean difference −0·005 to 0·002).

The mean slopes for $\log_e$ CRF were: normal ($n=80$) mean slope 0·224 (SD 0·118), abnormal ($n=81$) mean slope 0·265 (SD 0·129) and the difference was significant ($P<0·05$) (95% CI for the mean difference −0·08 to −0·003) (Fig. 1).

The mean slope for the normal group for both CRF and EDLI was compared with the PIH, APH and preterm delivery subgroups. There were no significant difference between the normal mean slopes and any subgroup (Table 3).

After adjustment for the variables age, race, previous PIH, placental weight, and number of previous pregnancies, the slopes for CRF were found not to be significantly related to outcome (normal or abnormal). In the regression model smoking, parity and age were significantly related to outcome ($P<0·001$).

The sensitivity, specificity and predictive value of the CRF slope were calculated using a cut off slope of ≥0·4 as abnormal. A value of 0·4 was chosen as it represents a reasonable cut off between normal and abnormal slopes (Fig. 2). The sensitivity was 17%, specificity 93% and predictive value of a positive test 70% (95% CI 50% to 90%).

Discussion

Maternal plasma CRF levels rise with gestational age, unlike most other placental peptides, other than PAPPA, which plateau in the third trimester. This may represent a role for CRF in the process of parturtion, especially as elevated levels have been reported in preterm labour

Table 1. Corticotrophin releasing factor (CRF) concentrations in normal and abnormal pregnancies from 24 weeks to term

	$\log_e$ CRF concentration (pg/ml)							
	Normal group ($n=80$)				Abnormal group ($n=88$)			
Gestation (weeks)	Mean	SD	Median	(*n*)	Mean	SD	Median	(*n*)
24	4·31	1·43	4·92	(64)	3·90	1·86	4·47	(57)
26	4·46	1·43	5·01	(57)	4·40	1·59	4·86	(50)
28	4·90	1·08	5·18	(52)	4·83	1·61	5·29	(39)
30	5·20	1·39	5·49	(48)	5·20	1·47	5·51	(51)
32	5·64	1·04	5·65	(45)	5·87	1·24	5·90	(51)
34	6·40	0·73	6·22	(46)	6·50	1·25	6·38	(44)
36	6·89	0·85	6·64	(37)	7·10	0·90	7·12	(39)
38	7·13	0·88	7·05	(38)	7·24	0·77	7·27	(15)
40	7·74	0·58	7·72	(17)	7·55	0·74	7·46	(9)

Table 2. Endogenous digoxin-like immunoreactivity (EDLI) in normal and abnormal pregnancies from 32 weeks to term

	EDLI concentrates							
	Normal group (n=80)				Abnormal group (n=88)			
Gestation (weeks)	Mean	SD	Median	(n)	Mean	SD	Median	(n)
32	0·08	0·07	0·08	(45)	0·12	0·14	0·10	(54)
34	0·13	0·09	0·13	(46)	0·20	0·20	0·13	(46)
36	0·14	0·07	0·17	(38)	0·20	0·16	0·17	(43)
38	0·18	0·10	0·18	(42)	0·19	0·09	0·19	(15)
40	0·25	0·11	0·23	(16)	0·33	0·29	0·22	(9)

(Wolfe *et al.* 1988). This is the first report of sequentially measured concentrations of EDLI during pregnancy and there is a significant rise in EDLI levels with gestational age. It has been observed that EDLI levels are elevated in preterm infants (Koren *et al.* 1984; Morris *et al.* 1987) and preterm deliveries (Wolfe *et al.* 1987) and correlate with birthweight leading to the suggestion that the hyponatraemia associated with preterm birth may be the result of a naturesis brought about by the high concentration of a digoxin-like substance. Only 15 preterm deliveries occurred in this study and for both CRF and EDLI the mean slopes were higher but not significantly different from normal in the preterm group.

Previously we have reported elevated levels of CRF in subjects with PIH (Wolfe *et al.* 1988) but it was not established whether this rise occurred before the development of hypertension. Again the number of subjects studied is small but there would appear to be no significantly steeper rate of rise of CRF in subjects with PIH compared to a normal subject. A number of reports (Gusdon *et al.* 1984; Graves *et al* 1984) have shown that EDLI is higher in hypertension but it is not known which substance or substances cause this elevation although it has been suggested that they may be the result of a compound with digoxin-like characteristics, including sodium transport inhibiting activity. Similarly to CRF, the slope of EDLI is steeper but not significantly so in the hypertensive group.

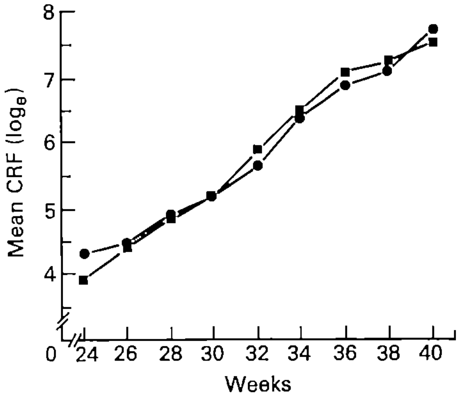

Fig. 1. A plot of mean corticotrophin releasing factor (CRF) (log$_e$) against gestation (in weeks) for normal —●— and abnormal —■— pregnancies

The prospective study which uses the individual slopes for EDLI and CRF in the third trimester overcomes the problem of the wide range of results at each gestational age if the data are analysed cross sectionally and reflect each woman's rate of rise per week. Logistic regression controls for other variables which may affect outcome. There appears to be no difference between normal and abnormal pregnancy for EDLI but there is for CRF, but when a logistic

Table 3. The mean slopes of endogenous digoxin-like immunoreactivity (EDLI) and corticotrophin releasing factor (CRF) in normal and abnormal pregnancy subgroups

		Slopes		
	Sample size (n)	Mean	SD	SE
EDLI				
Normal	79	0·013	0·007	0·008
PIH	20	0·015	0·017	0·004
APH	16	0·011	0·007	0·002
Preterm	15	0·019	0·02	0·005
Log$_e$ CRF				
Normal	80	0·224	0·118	0·013
PIH	20	0·255	0·096	0·021
APH	13	0·245	0·198	0·055
Preterm	12	0·279	0·139	0·040

PIH=pregnancy-induced hypertension
APH=antepartum haemorrhage

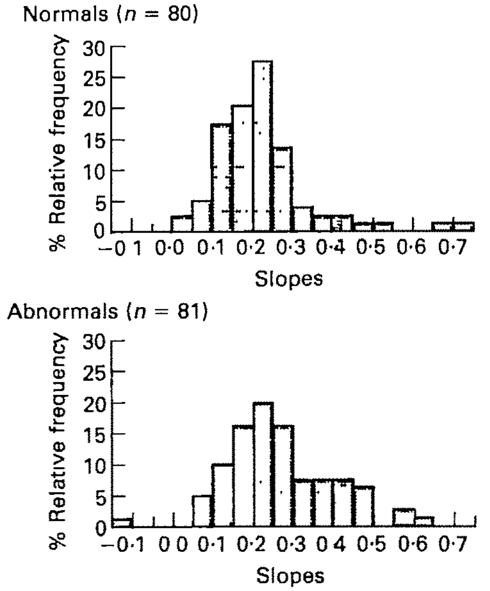

Fig. 2. Percent relative frequency of corticotrophin releasing factor (CRF) slopes for normal and abnormal pregnancies.

regression model is fitted with the outcome variable, normal or abnormal, CRF assumes no significant role. CRF may therefore be one of many factors predictive of abnormal outcome. There is a problem with analysis of the subgroups of abnormal pregnancy as the numbers are small, but in general the slopes are steeper, but not significantly so, for both EDLI and CRF in abnormal pregnancy states. Further prospective measurements in women who subsequently have abnormal pregnancy outcomes, such as PIH, APH and preterm labour, are required and the slopes of normal and each abnormal category compared.

This may provide information on the role of these substances in various abnormal states and the possibility of their measurement as a predictor of abnormal pregnancy outcome.

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Antepartum to postpartum changes in transcapillary fluid balance

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Summary. During the puerperium significant changes occur in the body volume homeostasis. In the present study the transcapillary fluid balance was examined antepartum in nine healthy women. The interstitial colloid osmotic pressure was measured by the 'wick' method, and interstitial hydrostatic pressure by the 'wick-in-needle' method in subcutaneous tissue on the thorax and at the ankle. From antepartum (gestational week 37–40) to postpartum (5th day), the following changes were observed: A significant increase in the colloid osmotic pressure both in plasma (mean 1·8 mmHg, P=0·027) and in the interstitial fluid at the ankle (mean 2·9 mmHg, P=0·008). Neither colloid osmotic pressure gradient (plasma-interstitium), interstitial hydrostatic pressure, nor haemoglobin and haematocrit changed. The observed rise in the interstitial colloid osmotic pressure must be caused by mobilization of fluid from the interstitium, probably due to a reduced capillary hydrostatic pressure. The increase in plasma colloid osmotic pressure is most likely caused by an increased albumin synthesis and/or transport of interstitial proteins back to the vascular compartment.

Pregnancy is a condition characterized by significant and complex alterations in body fluid homeostasis. During normal pregnancy, there is an increase in both the plasma and the interstitial fluid volume. The plasma volume is well regulated by hormones, volume- and osmo-receptors and renal salt and water excretion. The interstitial fluid is a fluid buffer as well as a transport medium for nutrients and waste products between blood and cells.

The interstitial fluid volume is regulated by the 'Starling forces' (Starling 1896), i.e., the capillary hydrostatic pressure (Πc), plasma colloid osmotic pressure (COΠp), interstitial fluid hydrostatic pressure (Πi) and interstitial fluid colloid osmotic pressure (COΠi) Among these factors, only COΠp is easy to measure. Methods are now available to measure the 'inaccessible tissue factors, Πi and COΠi in man (Fadnes *et al.* 1977, Noddeland *et al* 1982, Øian *et al.* 1985), and it is established that these methods give a good estimate of Πi and COΠi in undisturbed interstitial fluid (Aukland & Nicolaysen 1981).

Both the plasma albumin concentration and COΠp are reduced during normal pregnancy (Wu *et al.* 1983; Øian *et al.* 1985). A further decline has been observed immediately after delivery (Gonik & Cotton 1984). This has been attributed mainly to administration of intravenous crystalloid solutions during labour and immediately after delivery. In some patients COΠp has been reported to be dangerously low, and suggested as the mechanism of an increased

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risk of pulmonary oedema in the early postpartum period. This may also explain the observation that as many as 50% of chest radiographs in postpartum women demonstrate pleural effusions (Hughson *et al.* 1982).

In many clinical conditions with fluid retention, measurements of Πi and COΠi are of great importance for an understanding of the transcapillary fluid exchange; recently this has been shown both in normal pregnancy and in pre-eclampsia (Øian *et al.* 1985, 1986). The tissue factors Πi and COΠi have not been measured in the postpartum period In the present study transcapillary fluid balance was examined before and after delivery when the altered volume homeostasis observed during pregnancy will return towards the non-pregnant state.

Subjects and methods

Nine healthy women, four nulliparous and five parous with normal pregnancies were studied. Their mean age was 28·9 years (range 19–39). The mean antepartum body weight was 73·4 kg (range 60·5–85·0), the mean height 166 cm (range 163–173) and the mean weight gain 12·8 kg (range 7·5–20·7) Only two had slight oedema of their lower legs. All had normal blood pressure, and no proteinuria or renal disease. The patients studied experienced neither excessive blood loss, nor received any colloids or blood products. One woman was delivered by caesarean section due to ruptured membranes and persistent transverse position of the fetus. She was the only one who received crystalloids, and only on the first day postpartum (2 litres). Informed consent was obtained and the study was approved by a regional committee of medical research ethics.

Transcapillary fluid balance (COΠp, COΠi, Πi), serum albumin, and total protein concentrations were studied antepartum (gestational week 37–40) and on the 5th day postpartum. Haemoglobin and haematocrit were measured antepartum, and on the first, third and fifth day postpartum. The examinations were performed at between 0800 and 1100 hours. Blood samples were obtained from an antecubital vein without stasis after the woman had rested for 30 min in the supine position. Haemoglobin, haematocrit, serum albumin and total protein concentration were measured by AutoAnalyzer. Interstitial fluid was sampled by sewing 3–4 nylon wicks subcutaneously on the side of the thorax at heart level, and at the ankle approximately 10 cm above the lateral malleolus, after anaesthetizing the skin with lidocaine without adrenaline The wicks were left implanted for one hour, and the wick fluid was separated by centrifugation in mineral oil The colloid osmotic pressures were determined by a colloid osmometer designed for small fluid samples (5 µl), with a membrane impermeable to proteins with a molecular weight above 30 000 daltons (Noddeland 1982, Øian *et al.* 1985). The plasma colloid osmotic pressure was measured with the same colloid osmometer. The interstitial fluid hydrostatic pressure was measured by the 'wick-in-needle' method, described by Fadnes *et al.* (1977). A sterile needle filled with loose bundles of nylon filaments was connected to a pressure transducer by a saline-filled tube, and inserted subcutaneously at the level of the implanted wicks.

Statistical methods

Differences were evaluated by Wilcoxon signed rank test for paired data. *P* values < 0·05 were considered significant

Results

Both the plasma and the interstitial fluid colloid osmotic pressure at the ankle increased significantly on the 5th day postpartum in comparison with the antepartum period (Table 1). The individual changes are presented in Fig. 1. There was a slight, but insignificant increase in the thoracic interstitial fluid colloid osmotic pressures. The colloid osmotic gradient (COΠp–COΠi), the interstitial hydrostatic pressures, as well as serum albumin, and total protein concentration remained constant (Table 1). There was no significant change in haemoglobin and haematocrit through the first, third and fifth day postpartum (Fig. 2).

Discussion

This is the first study of transcapillary fluid balance in the postpartum period; the tissue factors COΠi and Πi have not been measured previously. Earlier studies have reported a decline in plasma colloid osmotic pressure from intrapartum to 8 and 24 h after delivery (Gonik & Cotton 1984, Cotton *et al.* 1984). These findings are not related to the route of delivery or anaesthetics used, but to the intravenous fluid given

Table 1. Antepartum to postpartum (5th day) changes in plasma colloid osmotic pressure (COΠp), interstitial colloid osmotic pressure (COΠi), interstitial fluid hydrostatic pressure (Πi), serum albumin and total protein concentration in nine women

	Group mean values		Individual differences between antepartum and postpartum		
	Antepartum	Postpartum	Mean	(SD)	Significance
COΠp (mmHg)	18·7	20·5	−1·8	(2·6)	$P = 0{\cdot}027$
COΠi (mmHg)					
Thorax	10·5	11·8	−1·4	(2·3)	NS
Ankle	5·5	8·4	−2·9	(2·2)	$P = 0{\cdot}008$
Πi (mmHg)					
Thorax	−1·9	−2·3	0·4	(2·0)	NS
Ankle	−1·4	−0·8	0·6	(2·3)	NS
Albumin (g/l)	32·3	33·7	1·4	(2·6)	NS
Total protein (g/l)	59·5	61·9	2·3	(4·4)	NS
Haemoglobin (g/dl)	11·9	11·9	0·0	(1·4)	NS
Haematocrit (%)	35·4	35·8	−0·4	(3·6)	NS

during labour and the immediate postpartum period. In the present study we examined transcapillary fluid dynamics antepartum and on the 5th day postpartum. Intravenous fluid was administered only to one woman, and only 2 litres of crystalloids the first day postpartum. No change in haemoglobin or haematocrit were found.

A significant increase in CoΠp and CoΠi at the ankle was observed from the antepartum period to the 5th day of puerperium. A significant blood loss occurs in all deliveries. To maintain blood pressure, total peripheral resistance increases, mainly due to a rise in pre-capillary resistance. This leads to a fall in the capillary hydrostatic pressure and fluid is mobilized from the inter-

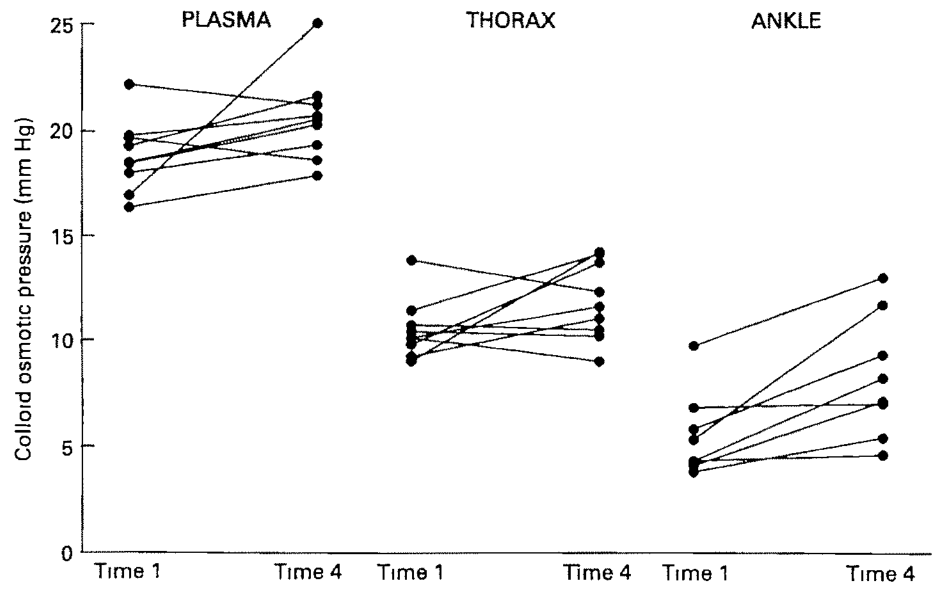

Fig. 1. Individual measurements of plasma and interstitial colloid osmotic pressures antepartum (Time 1) and on the fifth day postpartum (Time 4) in nine women.

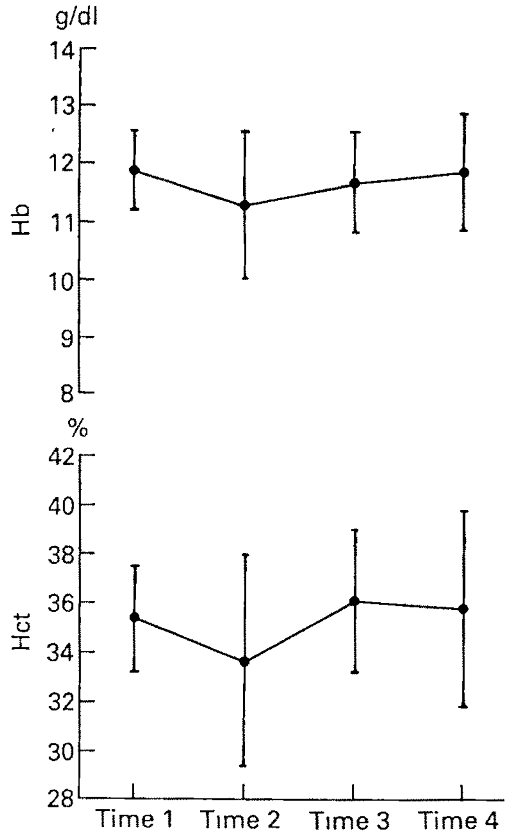

Fig. 2. Changes in haemoglobin (Hb) and haematocrit (Hct) from antepartum (Time 1), first day (Time 2), third day (Time 3), and fifth day postpartum (Time 4) in nine women Values represent mean ± SD.

stitial compartment Our finding of a significant increase in COΠi at the ankle on the 5th day postpartum may therefore be due to dehydration of the interstitium. The mobilized fluid is then eliminated via the kidneys by hormonal and renal mechanisms. Factors other than blood loss may also contribute to a reduced capillary pressure. It is known that during normal pregnancy total peripheral resistance is reduced, probably due to vasodilating agents such as prostaglandins. In the postpartum period this hormonal influence ceases, precapillary resistance increases and the capillary pressure is reduced.

In the present study haemoglobin and haematocrit were unchanged from antepartum to 5th day postpartum measurements. The increase in COΠp can therefore not be explained by haemoconcentration, but is most likely due to an increased albumin synthesis in the postpartum period and/or transport of interstitial proteins via the lymph back to the vascular compartment

The postpartum level of COΠp is still significantly lower than in the non-pregnant state (Øian *et al.* 1987). In spite of a significant increase in COΠp, the serum albumin and total protein concentrations showed only a slight and non-significant increase. This is in accordance with the knowledge that the relation between serum albumin concentration and COΠp is non-linear, with an exponential rise in colloid osmotic pressure when albumin concentration increases. The plasma colloid osmotic pressure is therefore sensitive to small changes in albumin concentrations (Landis & Pappenheimer 1963).

In conclusion, the colloid osmotic pressures in plasma and interstitial fluid at the ankle are significantly elevated on the 5th day postpartum compared with the antepartum period The increase in interstitial fluid colloid osmotic pressure is caused by fluid mobilization, and there is evidence for a reduced capillary hydrostatic pressure as the primary mechanism behind this fluid mobilization. The increase in plasma colloid osmotic pressure is most likely due to an increased albumin synthesis and/or transport of interstitial proteins back to the vascular compartment.

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Dipalmitoylphosphatidylcholine (L-α-lecithin) stimulates prostaglandin E production in human amnion

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Summary. The effect of dipalmitoylphosphatidylcholine (DPPC, L-α-lecithin), a substance not containing arachidonic acid, on prostaglandin E (PGE) production of amniotic membrane was studied. DPPC (3·125–800 μg/ml) stimulated PGE production of amniotic membrane (150–200%) , suggesting that lecithin, the major surfactant component, is directly involved in the mechanism of human parturition as a stimulator of PGE production.

The mechanism of onset of human parturition has been extensively studied without conclusive results. Prostaglandins (PGs) are known to be involved and both PGE_2 and $PGF_{2\alpha}$ can stimulate myometrial contractility. Fetal membrane, especially the amnion, is thought to be an important source of PGs (especially PGE_2) (Fuchs *et al.* 1981, Okazaki 1981; Yasumizu 1981; Rehnström *et al.* 1983, Tyson *et al.* 1985). There have been some reports of increased PGE_2 production by amniotic membrane after the onset of labour (Olson *et al* 1983, Manzai *et al* 1984), but the mechanism is still uncertain. Recently, López Bernal *et al.* (1988) reported that human amniotic fluid surfactant phospholipids increase PGE output of human amnion. They concluded that surfactant is a major source of arachidonic acid for PGE production, and suggested the possibility that surfactant stimulates endogenous PG production. Since lecithin constitutes 80–90% of surfactant phospholipids and 60–90% of its fatty acid is made up of palmitic acid (López Bernal *et al.* 1988), surfactant could be more than merely the substrate for increased PGE production. Therefore, we studied the effect of dipalmitoylphosphatidylcholine (DPPC, L-α-lecithin), which does not contain arachidonic acid, on PGE production of amniotic membrane to examine the possibility that lecithin increases PGE output as a stimulator, not as a substrate.

Materials and methods

Five placentas were obtained at term. All women were delivered of healthy singleton babies. Placental weight was 584 g (SD 207; range 390–930), gestational age was 273 days (SD 4; range 268–280), and maternal age was 29·8 years (SD 4·4; range 26–32). Informed consent was obtained from all women. Immediately after the birth of the placenta, amniotic membrane from a site opposite to the placenta was separated and cut into 3–5 pieces each measuring 4 cm^2 All specimens were washed gently several times with ice cold saline, and kept in ice cold saline until incubation.

Within 2 h of collection, all specimens were preincubated for 1 min at 37°C in 2·0 ml of Krebs-Ringer bicarbonate solution (pH 7·4) bubbled with 95% O_2 and 5% CO_2, then further incubated for 30 min under the same conditions with or without dipalmitoylphosphatidylcholine (DPPC, L-α-lecithin). DPPC was dissolved in the Krebs-Ringer solution by sonication. After incubation, specimens were weighed.

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Table 1. Cross-reactivity of anti-PGE_2

	Cross-reactivity (%)
PGE_2	100
PGE_1	63
13,14-dihydro-15-keto-PGE_2	0·26
PGB_2	57
$PGF_{2\alpha}$	1·4
TXB_2	0·023
6-keto-$PGF_{1\alpha}$	0.24

PGE_2 was extracted with Bond Elut C18 extraction cartridge column. Recovery rates was calculated using [^{3}H]-PGE_2 (about 1000 counts/min) added to each sample before extraction.

Authentic PGE_2 and its antiserum were kindly provided by Ono Pharmaceutical Co. Ltd. (Osaka, Japan) and radioactive PGE_2 was purchased from Amersham International plc (Amersham, Buckinghamshire, England). RIA method was as described by Yamaguchi & Mori (1985). Cross-reactivity of antiserum is shown in Table 1. Results are expressed as PGE because the antiserum does not distinguish between PGE_1 and PGE_2. The intra- and inter-assay coefficients of variation for PGE were 7·6% and 15·4%, respectively. All values were corrected for extraction losses (recovery rates). Production rate wsa expressed as pg/mg wet weight/min. Statistical analysis used the paired Student's *t*-test.

Results

The mean recovery rate was 95·2% (SD 5·7; range 76·5–100). Although basal PGE production varied with each sample of amniotic membrane, DPPC added to incubation medium significantly increased PGE production of each amniotic membrane (Table 2).

Increment ratios for each DPPC concentration of five amniotic membranes are shown in Fig. 1. PGE production increased with the increase of added DPPC. At the concentration of surfactant lecithin in term amniotic fluid (100–400 μg/ml), PGE production was 150–200% of basal PGE.

Discussion

DPPC stimulated PGE production of human amniotic membrane, and since DPPC does not contain arachidonic acid, the results of our study suggest for the first time that lecithin behaves as a stimulator of amniotic membrane PGE production rather than as a substrate. Variations in basal PGE production may be due to differences in the availability of endogenous arachidonic acid (López Bernal *et al.* 1988).

A number of factors which regulate PGE_2 production in amniotic membrane have been reported. Among stimulators are oxytocin (Fuchs *et al.* 1981), β-stimulant (Di Renzo *et al.* 1984), platelet-activating factor (PAF) (Billah *et al.* 1985), relaxin (López Bernal *et al.* 1987), endotoxin (Romero *et al.* 1988), epidermal growth factor (EGF) (Casey *et al.* 1988), transforming growth factor (TGF) (Mitchell *et al.* 1988), interleukin-1 (Romero *et al.* 1989) and

Table 2. Effect of dipalmitoylphosphatidylcholine (DPPC) on prostaglandin E (PGE) production by pieces of amniotic membrane obtained from five women delivered at term.

Subject no.	No. of pieces	PGE production (pg/mg wet weight/min) with these concentrations of DPPC (μg/ml)									
		0	3·125	6·25	12·5	25	50	100	200	400	800
1	3	0·76	–	–	–	–	*1·31*	1·20	*1·91*	*1·64*	*1·71*
		(0·19)	–	–	–	–	(0·04)	(0·64)	(0·63)	(0·47)	(0·60)
2	3	1·49	–	–	–	–	2·70	*2·69*	*2·92*	*2·18*	*2·31*
		(0·12)	–	–	–	–	(0·92)	(0·76)	(0·84)	(0·38)	(0·52)
3	5	2·09	3·07	2·72	*3·61*	*3·50*	2·99	*4·16*	*4·15*	*4·86*	3·68
		(0·55)	(1·60)	(1·66)	(1·12)	(1·07)	(1·17)	(1·31)	(1·31)	(1·37)	(1·48)
4	5	3·22	3·89	*6·15*	*5·27*	*5·79*	*6·44*	*6·47*	4·50	*5·37*	*7·06*
		(0·72)	(1·97)	(2·11)	(0·85)	(1·54)	(1·44)	(0·98)	(2·35)	(0·89)	(1·93)
5	5	0·83	0·96	*1·21*	*1·34*	*1·41*	*1·39*	*1·46*	*1·92*	*1·65*	*1·71*
		(0·14)	(0·12)	(0·23)	(0·23)	(0·16)	(0·17)	(0·29)	(0·32)	(0·17)	(0·24)

The results are shown as mean (SD) values, the numbers in italics denote mean values statistically significantly higher than the basal value for each respective sample.

As in the first two amniotic membranes the concentration of DPPC tested (⩾50 μg/ml) showed sufficient stimulation, the effect of lower concentrations was studied in the other three samples.

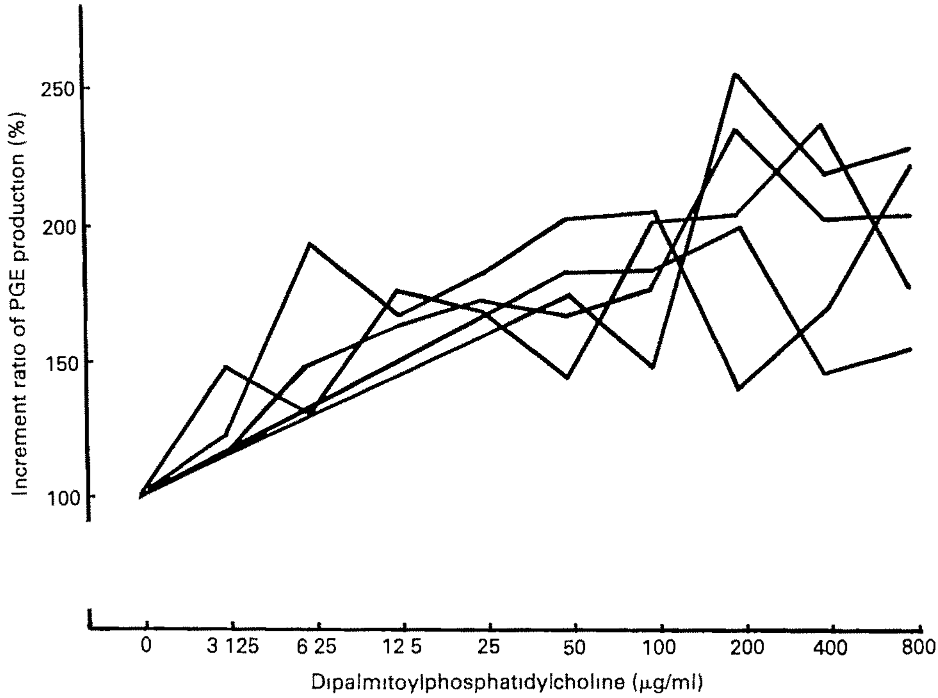

Fig. 1. Increment ratios expressed as percentages of basal prostaglandin E (PGE) in five amniotic membranes stimulated by dipalmitoylphosphatidylcholine in vitro

other stimulators of amniotic fluid (Rehnström *et al.* 1983; Stickland *et al.* 1987). Among inhibitors are prolactin (Tyson *et al* 1985), relaxin (López Bernal *et al* 1987) and other inhibitors of amniotic fluid (Wilson *et al.* 1985). The stimulators were reported to need higher concentrations than physiological ranges in amniotic fluid in order to increase PGE_2 output. Among many substances known to evoke increased PG synthesis, only murine EGF has been reported to cause a striking effect on PGE_2 formation by human amnion cells in culture (Casey *et al.* 1987). Concentration of EGF in their experiments (10–15 ng/ml) was much higher than that in the term amniotic fluid (0·5 ng/ml) reported by Haigh *et al.* (1989). It is notable that in our experiment the stimulating effect of surfactant lecithin was observed in the same physiological concentrations as occurs in term amniotic fluid (below 400 μg/ml) reported by Oulton *et al.* (1979). Concerning the involvement of this phenomenon in the onset of parturition, it does not seem that the surfactant in amniotic fluid directly causes the rapid increase of PGE_2 production that leads to labour because surfactant lecithin in amniotic fluid increases from 33–34 weeks gestation with fetal lung maturation and thereafter there is no marked change until before labour (Gluck *et al.* 1973) Nevertheless, lecithin acts as a stimulator and may play some part in the mechanism of human parturition by activating amniotic membrane to increase PGE_2 production.

As DPPC also stimulates leukotriene C_4 and/or D_4 production by guinea pig lung (data not shown), the first possible mechanism of stimulation is direct activation of phospholipase by DPPC. The second possible mechanism may be activation of prostaglandin endoperoxide synthase or PGE synthase. Stimulation also may occur through other factors such as 5-lipoxygenase metabolites, because 5-lipoxygenase metabolites are reported to increase cyclooxygenase metabolite production (6-keto $PGF_{1\alpha}$, TXB_2) (Clark *et al.* 1986).

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Vitamin B6 in the treatment of the premenstrual syndrome—a review

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Summary. A search of the literature yielded 12 controlled trials on vitamin B6 in the treatment of the premenstrual syndrome. These are discussed with emphasis on methodological aspects. A major drawback of the trials is the limited number of patients included. The existing evidence of positive effects of vitamin B6 is weak, and some well-designed trials with positive results would be needed to change this view.

Many theories on the aetiology of the premenstrual syndrome (PMS) have been proposed, including speculation about the effects of hormonal imbalances involving oestrogen, progesterone and prolactin, and about neuroendocrine dysfunction. Dysfunction of the pituitary gland production of endogenous opiates and/or α-melanocyte-stimulating hormone might explain most of the symptoms (Reid & Yen 1981). An alternative explanation might be decreased sensitivity of progesterone receptors in several organs. In any event, no generally accepted explanation of the aetiology currently exists.

Various therapies have been advocated in the treatment of PMS. One of them is the use of megadoses of vitamin B6 (pyridoxine). Pyridoxal 5′ phosphate, the active form of vitamin B6, serves as the coenzyme of a wide variety of enzymes of amino acid metabolism (Friedrich 1988) It serves for instance as a cofactor in the metabolism of tryptophan (the precursor of serotonin), and also in the metabolism of tyrosine (leading to dopamine and noradrenalin) and glutamate (leading to gamma-aminobutyric acid). Low levels of dopamine and serotonin lead to high levels of prolactin and aldosterone, explaining the fluid retention. Against this background, postulation of beneficial effects of vitamin B6 supplementation on both physical (fluid retention) and psychological (effect on neurotransmitters) symptoms related to PMS seems reasonable.

However, implementation in regular practice can only be considered if clinical practice shows positive results. In a survey of 282 randomly chosen general practitioners in the Netherlands, 36% reported that they believed in the efficacy of vitamin B6 in PMS (Knipschild *et al.* 1990). The best way to show its efficacy is, of course, to perform randomized, placebo-controlled trials. The trials found after searching the literature are reviewed here.

Materials and methods

Identification and selection of relevant studies

Trials were only eligible if an index and a control group were included and if vitamin B6 was given to one of the treated groups. Controlled studies in animal models were excluded. Experiments were found by screening Index Medicus from 1966 to 1989 (keywords: pyridoxine-administration-and-dosage and pyridoxine-therapeutic-use), and by screening Excerpta Medica, section 10 (Obstetrics and Gynecology) from 1966–1989 (keywords: pyridoxine and vitamin B6). Further experiments were found by checking references extensively and by personal communication with authors of experiments. We also visited Hoff-

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man-La Roche, in Basel, in an attempt to ascertain unpublished studies.

We found 10 randomized double-blind trials on the effects of vitamin B6 in patients with PMS. In two other double-blind trials the effect of vitamin B6 on premenstrual mastalgia was studied. These 12 studies are listed in Table 1 and are considered in detail in Tables 2 and 3.

One study (Day 1979) was excluded because it is not really a cross-over study (no random allocation; all patients received vitamin B6 during cycle 2, 3 and 4 and placebo during cycle 1, 5 and 6). Another study was excluded because only one woman was treated (Mattes & Martin 1982). These two studies both suggested positive results of vitamin B6 treatment.

Assessment of methodological quality of published studies

General criteria such as comparability of the treatment groups (prestratification, randomization), the interventions (adequate placebos) and the effect measurements (double blinding) should be met in every therapeutic trial. Special attention must be paid to some specific aspects of trials on PMS. The predominant symptoms of PMS are abdominal bloating, breast pain or tenderness, headache, oedema, fatigue, depression and irritability, starting somewhere in the second half of the cycle, with relief at or soon after the onset of menstruation. A clear definition of PMS does not exist, thus authors of trials should indicate what their inclusion criteria were and which symptoms were assessed in their investigation. An overall, global index of the complaints appears appropriate, since the impact of individual symptoms on the total discomfort may vary from patient to patient. An adequate description of the way in which these symptoms have been assessed (which questionnaire on depression, which scales for the assessment of pain etc.) is also important

Furthermore, it is advisable to extend the investigation over several cycles, especially in experiments with a limited number of patients, since there may be considerable variability of the severity of the symptoms both within patients in different cycles and between patients.

To explore the possibility that an increasing likelihood of bias (with an increasing number of shortcomings) is reflected in the results of the trials, we used the following criteria for a methodological assessment of the experiments: (A) Characteristics of the women adequately described (description of symptoms, duration, severity, and previous treatments). (B) At least 50 women in each group. (C) Prestratification (matching) on relevant prognostic factors. (D) Randomization. (E) Check of prognostic comparability. (F) Subjects blinded. (G) Assessors blinded. (H) Effect measurements well described (reproducible). (I) Use of other concurrent treatments or vitamins has been checked and (J) presentation of the results in such a manner that the analysis can be checked by the reader.

It could be argued that other criteria should be used for the methodological assessment. However, we have selected well established methodological criteria, as have been described by Meinert (1986), and our assessment can be checked by the reader (Table 2).

Results

The main characteristics and results of the studies are summarized in Table 1.

The dosages which were used varied from 50 mg to 500 mg pyridoxine a day (the recommended daily allowance in healthy adults is 2 mg/day). No relation to the results of the experiments can be seen regarding different dosage levels. The duration of the experiments varied from 1 to 12 cycles; most experiments lasted 2 or 3 cycles. Individual symptoms, or scales assessing many symptoms, e.g., 47 in a scale developed by Moos (1969), were mostly used for the measurement of the treatment effects. These were in general reasonably well described. However, the number of women, mostly 20–40 in each group, was limited. The only exception is the multi-centre study reported by Williams *et al.* (1985) (200 patients in each group). Overall treatment effects additional to the assesment of individual symptoms were measured in only three trials (Barr 1984, Hagen *et al.* 1985 and Williams *et al.* 1985). Only trivial or no side effects were reported in the studies presented.

Abraham & Hargrove (1980), Barr (1984) and Hallman (1987) reported positive effects, but generally the symptoms did not disappear completely. Stokes & Mendels (1972), Williams *et al.* (1985), Smallwood *et al.* (1986), Kendall & Schnurr (1987), and Doll *et al.* (1989) found ambiguous effects; overall the results of these studies were disappointing. Colin (1982), Hagen

Table 1. Characteristics of controlled trials of vitamin B6 in the treatment of the premenstrual syndrome

Study	Entry criteria	Number and design	Daily dosage (mg)	No. of cycles,* effect measures	Outcome data
Positive result					
Abraham & Hargrove (1980)	Moderate to severe symptoms, no Medication and no OC	25 Cross-over	500	2* 3, 19 symptoms	Significant B-6 effect in excess of placebo effect in 21 subjects
Barr (1984)	— (most patients were not on any OC)	36 Cross-over	100	2* 2, 8 symptoms	Improvement for 83% on B-6 and 28% on placebo
Hallman & Oreland (1987)	Severe symptoms, no hormonal therapy	32 Cross-over	300	2* 4, 14 symptoms	Significant improvements found for 8 symptoms
Ambiguous result					
Stokes & Mendels (1972)	Premenstrual tension, depression	13 Cross-over	50	8–12, 47 symptoms	Not clear, 'disapppointing'
Williams *et al.* (1965)	Medication and OC were allowed	204/230 Parallel	100	3, 9 symptoms	Improvement for 82% on B-6 and 70% on placebo
Smallwood *et al.* 1986)	Premenstrual mastalgia, paracetamol was allowed	42, Cross-over	200	2* 2, pain, tenderness	No significant improvement; positive trend for tenderness on B-6
Kendall & Schnurr (1987)	Moderate to severe symptoms, no medication and no OC	29/26 Parallel	150	2, 47 symptoms	Significant amount of symptomatology remained (positive for behaviour, dizziness and nausea)
Doll *et al.* (1989)	Moderate to severe symptoms, no medication, OC were allowed	32, Cross-over	50	2* 3, 9 symptoms	Significant beneficial effect on emotional symptoms, no effect on other symptoms
Negative result					
Colin (1982)	— Mastalgia	17/15 Parallel, random?	500	2–4 months, pain, temperature	Improvement for 59% on B-6 and 60% on placebo
Hagen *et al.* (1985)	No medication and no OC	34, Cross-over	100	2* 2, scale of 6 symptoms	Improvement for 4% on B-6 and 21% on placebo using visual analogue scale
Malmgren *et al.* (1987)	No medication and no OC	19, Cross-over, random?	300	2* 1, many symptoms	No significant improvement of symptoms
Van den Berg *et al.* (1989)	No medication and no OC	34/42 Parallel	120	4, 47 symptoms	No difference

* 2* K = two periods of K cycles (cross-over).
OC = oral contraceptives.

et al. (1985), Malmgren *et al.* (1987), and Van den Berg *et al.* (1989) could not find any positive effects.

Table 2 shows that all trials had at least two methodological shortcomings. The mean 'score' for the trials with positive, ambiguous and negative results is 4·5, 6·2 and 4·1 respectively (maximum is 10), indicating that there is no trend in any direction according to the likelihood of bias (number of methodological shortcomings).

Table 2. Methodological score assigned to the 12 trials

	Methodological criteria										
Study	A	B	C	D	E	F	G	H	I	J	TOT
Positive result											
Abraham & Hargrove (1980)	±	–	–	+	+	+	+	+	–	+	6·5
Barr (1984)	–	–	–	+	–	+	+	–	–	–	3
Hallman & Oreland (1987)	±	–	–	+	–	+	+	±	–	–	4
Ambiguous result											
Stokes & Mendels (1972)	–	–	–	+	–	+	+	–	–	–	3
Williams *et al.* (1985)	±	+	±	+	–	+	+	+	+	+	8
Smallwood *et al* (1986)	±	–	–	+	+	+	+	–	+	+	6·5
Kendall & Schnurr (1987)	±	–	+	+	+	+	+	+	–	±	7
Doll *et al.* (1989)	+	–	–	+	±	+	+	+	–	+	6·5
Negative result											
Colin (1982)	–	–	–	±	–	+	+	–	–	–	2.5
Hagen *et al.* (1985)	±	–	–	+	–	+	+	+	–	±	5
Malmgren *et al.* (1987)	+	–	–	±	–	+	+	–	–	–	3·5
Van den Berg *et al* (1989)	±	–	–	+	+	+	+	+	–	–	5.5

Explanation of scores: +, item is scored; –, item is not scored, ±. item is partly scored; TOT, number of items which were scored.

A, Characteristics of subjects adequately described (description of symptoms, duration, severity, and previous treatments); B, at least 50 women per group; C, prestratification (matching) on relevant prognostic factors; D, randomization, E, check of prognostic comparability, F, subjects blinded; G, assessor blinded; H, effect measurement well described (reproducible), I, use of other concurrent treatments or vitamins has been checked; J, presentation of the results in such a manner that the analysis can be checked by the reader.

Table 3 shows which symptoms improved and which symptoms were not influenced by vitamin B6 treatment in the trials reporting on individual symptoms. The variation between trials turns out to be large and no trends are visible.

Discussion

Although PMS is prevalent among women of child bearing age, the number of participants in most studies was disappointingly low. Furthermore, compliance, blinding and prognostic comparability was checked in only 3, 0 and 1 trials respectively.

It could be argued that in cross-over studies fewer subjects need to be admitted because each subject serves as her own control. In these designs, however, the basic assumption that the women are prognostically comparable at the cross-over to the alternative treatment may not be met (inadequate washout, carry-over effects) In the eight cross-over studies considered in this review only Hallman & Oreland (1987) and Hagen *et al.* (1985) included washout periods, unless one assumes that the post menstrual phase of 2 weeks is sufficient to assure prognostic comparability of the groups at the beginning of the second treatment phase. Estimation of the bias introduced by carry-over effects is very difficult. Interestingly of the four studies with a parallel group design, two showed negative results and two ambiguous results. All positive assessments resulted from cross-over studies.

We did not pool the results of the trials. The methodological quality must obviously be high before statistical pooling makes sense More-over, there were differences in the characteristics of the women, the dosage of vitamin B6, the duration of the intervention and the outcome measurements.

Publication bias is important in every review article. Trials with negative results are less likely to be submitted and published than trials with positive results, especially if limited numbers of subjects have participated. This might well be the case for trials of vitamin B6 in PMS. The magnitude of this bias is difficult to estimate.

Table 3. The effects of vitamin B6 on symptoms of the premenstrual syndrome

Study	Positive effects	No difference
Hagen *et al.* (1985)		Depression, irritability, bloatedness, weight gain, headache, breast tenderness, fatigue
Williams *et al.* (1985)		Depression, irritability, swelling/bloating, headache, breast tenderness, tension, violent feelings, coordination
Smallwood *et al.* (1986)	Breast tenderness	Breast pain
Kendall & Schnurr (1987)	Dizziness, nausea, poor performance, social activities	Many including: depression, anxiety
Hallmann & Oreland (1987)	Depression, irritability, swollenness, headache, hyperactivity, clumsiness, skin/hair changes	Tension, anxiety, apathy, sleeplessness, tiredness, appetite
Van den Berg *et al.* (1989)		Many including: depression, irritability, bloating, weight gain, headache, mastalgia, tension, anxiety
Doll *et al.* (1989)	Depression, irritability, tiredness	Swollenness, headache, breast discomfort, stomach cramps, backache

No positive or ambiguous effects of vitamin B6 have been observed in controlled trials on related subjects, such as the treatment of depression related to the use of oral contraceptives (Adams *et al.* 1973, Adams *et al.* 1974), inhibition of lactation (Foukas 1972, Foukas 1973, Macdonald *et al.* 1976, Canales *et al.* 1976), and in nausea and vomiting of pregnancy (Hesseltine 1946, General Practitioner Research Group 1963, Hillman *et al.* 1963).

In future studies, with larger groups of women, more attention must be paid to assuring prognostic comparability of the treatment groups, and to checking of compliance and blinding. A question remains about which dose of the vitamin should be used, what the optimal duration of treatment is, and whether perhaps only special subgroups (e.g., with relative deficiencies of vitamin B6) might benefit from vitamin B6 supplementation. At the moment there is no evidence that vitamin B6 is efficacious in the treatment of patients with PMS.

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Laparoscopic relief of adnexal torsion in early pregnancy. Case reports

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Case reports

Patient no. 1

A 34-year-old woman who had had three children presented at the emergency room because of lower abdominal pains of 2 days duration. She was tender and had guarding in the right lower abdomen. On vaginal examination the uterus was enlarged to the size of an 8 weeks pregnancy and she had a very tender, cystic mass in the right adnexa. The white blood cell count was mildly elevated ($10{\cdot}2 \times 10^9$/l).

Ultrasound examination showed a normal left adnexa and there was an intrauterine gestation sac containing a live fetus measuring 10 mm from crown to rump. The right ovary contained a smooth-walled unilocular cyst (13 × 10 × 10 cm). No free fluid was seen in the pouch of Douglas. Because of the possible diagnosis of torsion of the right adnexa the patient had a laparoscopy which showed a normal uterus, enlarged equivalent to 8 weeks pregnancy, and a normal left adnexa. On the right side the oedematous, pale tube and the ovary, enlarged by a 13 cm diameter cyst, had undergone 360° of torsion. A probe and a needle were introduced through two separate suprapubic punctures. The adnexa were untwisted in two stages. First, the contents of the cyst (120 ml of clear liquid) were aspirated, making the adnexa smaller and more amenable to mobilization. The needle was then replaced by a second probe and the tube-ovarian complex was untwisted by simultaneously pushing and pulling with the two probes.

The tube and ovary regained normal colour and were appropriately located in the pouch of Douglas. After two uneventful days in hospital the patient returned home. The cystic fluid did not contain any malignant cells on cytological examination The pregnancy progressed uneventfully and led to the spontaneous birth at term of a healthy girl weighing 3200 g.

Patient no. 2

A 22-year-old woman in her first pregnancy came to the emergency room because of lower abdominal pain of a few hours duration. She had been treated for primary infertility by her family physician with clomiphene citrate 150 mg/day for 5 days and hCG, 10 000 units. At the time of presentation she was in the late luteal phase. The pain had begun suddenly and was colicky, intermittent, of a few minutes duration. She was obviously in pain but there were no signs of peritoneal irritation. Vaginal examination revealed a normal size uterus and a slightly enlarged left ovary. On the right side, very close to the uterus, there was a very tender irregular mass, movement of the cervix caused exacerbation of the pain. She was afebrile. The haemoglobin level was 13·3 g/dl and the white blood cell count was $6{\cdot}3 \times 10^9$/l. Transvaginal ultrasound examination showed an empty uterus and a right multilocular ovarian cyst measuring 8·6 × 7.8 cm. The clinical picture suggested a diagnosis of twisted, hyperstimulated ovary. The patient underwent a laparoscopy. The left ovary contained a fresh corpus luteum and the uterus was normal. The cyst in the right ovary appeared pale, with a smooth external surface, 8–10 cm in diameter. The ovarian ligament and the tube were twisted.

A probe and a needle were introduced through a second suprapubic puncture and, by

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the same technique described for the first patient, the cyst was aspirated and the adnexa was returned to the normal position. The post operative period was uneventful. An hCG test on day 30 indicated pregnancy. The pregnancy had reached 26 weeks gestation with no further problems at the time of preparation of this case report.

Comments

Torsion of one or more components of the adnexa is an emergency situation. The clinical picture varies from intermittent abdominal pain as a result of incomplete or recurrent partial torsion to that of an acute abdomen if the torsion is complete. The potential danger of adnexal torsion is the permanent destruction of the organs involved The recommended treatment is immediate laparotomy, with removal of the organ when necrosis is evident. Simple untwisting of the adnexa is not recommended because of possible risk of thrombo-embolism (Nichols & Julian 1985) and infection of any necrotic tissue. Bider *et al.* (1989) were among the first to challenge the view that untwisting a necrotic adnexal mass is contraindicated. They described six pregnancies in which they untwisted necrotic or haemorrhagic adnexal masses with no complications.

The incidence of ovarian cysts during the first half of pregnancy was observed to be 1 in 190 by Hogston & Lilford (1986). The presence of an ovarian cyst predisposes the adnexa to torsion. Rodin (1989) has proposed ultrasound guided needle aspiration of simple cysts during pregnancy.

Ultrasound may suggest the diagnosis of adnexal torsion (Helvie & Silver 1989) but most authors consider laparoscopy an essential step for the diagnosis of this condition (Nichols & Julian 1985).

We present two examples of adnexal torsion during early pregnancy. In both, ultrasound examination suggested torsion. Laparoscopy was used to establish the diagnosis and for the definitive treatment. Pregnancy continued uneventfully in both women. We recommend aspiration of the cyst before detorsion is attempted, as it is easier to rotate the smaller masses and the risk for recurrent torsion, albeit small, is reduced.

In our view, laparoscopic detorsion of adnexa should be considered as a primary treatment for this condition. The procedure is of great value in girls and young women in whom the preservation of fertility is a major concern. The basic requisites for its use are a competent surgeon familiar with operative laparoscopy and close postoperative observation.

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Bilateral squamous cell carcinoma of the ovary. Case report

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Case report

A 64-year-old multiparous woman presented with vague lower abdominal pain and swelling, associated with constipation and weight loss over 5 months. Her past medical history included diabetes mellitus, pulmonary tuberculosis and a cerebrovascular accident causing right hemiplegia and dysphagia.

Examination showed features of right hemiplegia and slight conjunctival pallor. There was a hard, irregular pelvic-abdominal mass equivalent in size to about 16 weeks gestation. There were no dilated veins, skin metastasis or ascites. Pelvic examination confirmed the presence of a hard, irregular, fixed mass that could not be distinguished from the uterus. The cervix felt normal, but was fixed high behind the symphysis pubis.

Investigation revealed normocytic anaemia (Hb 8·9 g/dl, MCV 82 fl). Blood chemistry, liver function tests, chext X-ray and intravenous urography were all within normal limits. Ultrasound showed a normal liver, no ascites and an irregular, large mass occupying most of the pelvis. Barium enema showed indentation of the sigmoid colon.

After full bowel preparation, laparotomy was undertaken. This revealed an inoperable 'frozen pelvis' with large, fixed, bilateral ovarian tumours, metastatic seedlings on the peritoneum, liver and bowel surfaces and enlarged paraortic lymph nodes. The transverse, descending and sigmoid colon were adherent to the pelvic tumour and there was marked bowel distension, indicating subacute large bowel obstruction. Omentectomy was carried out and the large bowel was freed from adhesions to the tumour. A diagnosis of Stage IV ovarian carcinoma was made.

Histological examination of the omentum showed a metastatic poorly differentiated, necrotic, squamous cell carcinoma. Examination of the peritoneal fluid revealed clumps of neoplastic squamous cells. A course of chemotherapy was planned but the patient died, due to respiratory failure, 9 days after surgery.

Autopsy revealed massive pulmonary oedema and recent myocardial ischaemia. The abdominal cavity contained 600 ml of haemorrhagic fluid. There was a large pelvic mass adherent to the pelvic wall. Careful dissection showed that both ovaries contained lobulated, partly cystic and partly solid tumour with extensive necrosis, measuring about 15×10×10 cm on the right side and 13×12×8 cm on the left side. Both ovarian tumours infiltrated the uterine and bladder walls but the endometrium, cervix and bladder mucosa were normal. Extensive sampling of the ovarian masses showed a necrotic, poorly differentiated, squamous cell carcinoma with individual cell keratinization and small occasional keratin pearls. No evidence of teratoma, Brenner tumour, or endometriosis was seen. The endometrium was atrophic and the cervix and bladder mucosa were histologically unremarkable. In the absence of any other genital or extragenital primary site, we conclude that this case represents a bilateral ovarian squamous cell carcinoma.

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Discussion

We believe our patient represents the first report of bilateral squamous carcinoma of the ovary. A full post mortem examination, and subsequent microscopical examination, showed no evidence of other primary carcinoma within or beyond the genital tract. The available literature includes very few examples of primary squamous carcinoma of the ovary (Macko & Johnson 1983); most reported cases have been squamous carcinoma arising from either cystic teratoma, Brenner tumour (Shingleton *et al.* 1974; Scully 1982), or ovarian endometriosis (Piver *et al.* 1978). The most common sources of metastatic squamous carcinoma of the ovary are the cervix, vagina, bladder, skin, bronchus and oesophagus (Shingleton *et al.* 1974). In the absence of any such source of squamous carcinoma, it can be assumed that primary squamous cell carcinoma has arisen from the ovarian surface epithelium, which exhibits Mullerian differentiation as it undergoes neoplasia (Scully 1982). Mullerian type epithelium is capable of squamous differentiation and squamous elements are seen in endometroid tumours and rarely in mucinous and Brenner tumours,. Ultrastructural evidence suggests that some of the rare epidermoid cysts of the ovary arise by metaplasia of coelomic epithelium and a primary squamous cell carcinoma may represent a malignant counterpart (Nogales & Silverberg 1976). In advanced disease as described in our patient, the source cannot be identified with certainty but in the absence of Brenner tumour, endometriosis and epidermoid cyst, we postulate that the tumour was probably of surface epithelium origin. The number of reported patients with squamous cell ovarian carcinoma is too small to allow any valid conclusion regarding the epidemiology or aetiology (Macko & Johnson 1983). Bilateral ovarian tumour may be due to multicentric origin or the tumour may be unilateral initially, with subsequent spread to the opposite ovary as part of extension throughout the pelvis (Scully 1982). Most reported patients have shown poor survival (Tetu *et al.* 1987) after combination of surgical, radiation and chemotherapy treatment due to the aggressive nature of the tumour, inadequate surgical removal, advanced stage at the time of diagnosis. Our patient had a poor outcome, not only because of the advanced stage of the disease and poorly differentiated tumour, but also because of her poor general condition.

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SHORT COMMUNICATIONS

Serum ionized calcium and intact parathyroid hormone levels during pregnancy and postpartum

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A number of physiological events—all of which tend to lower maternal calcium concentration—occur during pregnancy (Pitkin 1985). Calcium homeostasis has been extensively studied in pregnancy. However, due to the use of insensitive methods and cross-sectional designs controversy still exists as to the changes in calcium and parathyroid hormone (PTH) levels (Pitkin 1985; Davis *et al.* 1988). This is a serial study of parathyroid function in pregnancy and during the first postpartum year. We used a new immunoradiometric assay for the intact and presumably active form of PTH

Methods and results

We studied 20 healthy women with a median age of 29 years (range 20–38). None had known parathyroid disease and none took medication with influence on parathyroid function. All women gave informed consent for participation in the study and the protocol was accepted by the regional ethics committee. Blood samples were obtained at 18, 24, 30 and 36 weeks gestation and at 1 and 12 months post partum.

Serum normalized ionized calcium (pH 7·4) levels were determined using an ICA calcium ion electrode (Radiometer, Copenhagen, Denmark). Serum intact PTH levels were determined using a commercially available two site immunoradiometric assay (Allegro-Nichols Institute, San Juan Capistrano, U.S.A.) (Nussbaum *et al.* 1987). The sensitivity was 1 ng/l and the intra- and inter-assay coefficients of variations were 5 and 7%, respectively. The normal reference range is 10–50 ng/l. For statistical analyses Student's *t*-test for paired data was applied. The general linear model was used for two-way analysis of variance due to unbalanced data, few observations were missing.

Fig. 1 shows the serum levels of ionized calcium during pregnancy and postpartum. Mean serum ionized calcium level showed a slight but significant decrease after 30 weeks gestation from 1·20 (SD 0·04) to 1·17 (SD 0·04) mmol/l ($P<0{\cdot}002$), and a similar small decrease from a mean of 1·20 (SD 0·05) to 1·16 (SD 0·04) mmol/l was observed postpartum ($P<0{\cdot}0001$) The mean serum PTH level rose significantly during pregnancy from 9·6 (SD 3·6) ng/l at 18 weeks gestation to 22·4 (SD 10·6) ng/l at 36 weeks ($P<0{\cdot}0001$). A significant increase in mean serum PTH level from 15·9 (8·4) ng/l to 27·3 (10·0) ng/l was observed by 12 months postpartum ($P<0{\cdot}001$).

Discussion

Most studies have demonstrated declining serum total calcium levels in pregnant women, whereas serum ionized calcium levels change minimally, if at all (Pitkin 1985). In contrast, considerable controversy exists regarding the effects of pregnancy on maternal PTH. Most studies of PTH have supported the concept of a physiological hyperparathyroidism of pregnancy with higher levels in pregnant than in nonpregnant women and with increasing levels during pregnancy (Pitkin 1985). However, unaltered and even lower levels of PTH in pregnant

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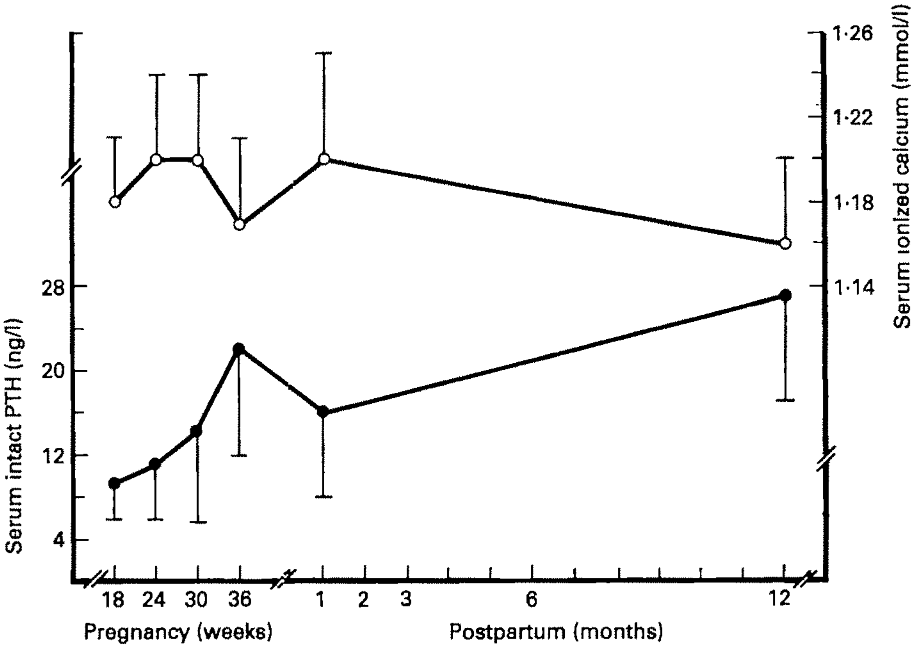

Fig. 1. Serum levels (mean±SD) of ionized calcium (○——○) and intact PTH (●——●) in 20 healthy women during pregnancy and postpartum.

women have been reported (Steichen *et al.* 1980; Whitehead *et al.* 1981; Gertner *et al.* 1986).

Employing an immunoradiometric assay for PTH highly specific for the intact, and presumably biologically active, form of PTH (PTH −(1–84)) in a longitudinal study we were not able to support the suggested concept of a physiological hyperparathyroidism during pregnancy. Assuming that values obtained 12 months postpartum represent the normal nonpregnant values for these women, pregnant serum PTH levels—although increasing during pregnancy—were always lower than postpartum levels. Our results are comparable with those recently obtained by Davis *et al.* (1988) in a cross-sectional study.

The present study is in keeping with other calcitropic factors than PTH being responsible for the maintenance of maternal calcium homeostasis. Thus, 1,25-dihydroxy vitamin D (1,25-$(OH)_2D$) known to increase during pregnancy has been suggested as the primary mediator of changes in maternal calcium metabolism (Gertner *et al.* 1986). Supporting this concept it has been reported that patients with pseudohypoparathyroidism requiring vitamin D therapy to compensate for their impaired renal capacity to synthesize 1,25 $(OH)_2D$ did not need such treatment to maintain normal serum 1,25 $(OH)_2D$ and calcium levels during pregnancy (Breslau and Zerwekh 1986).

In conclusion, pregnancy is not associated with a state of physiological hyperparathyroidism.

Acknowledgments

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Anxieties in women undergoing colposcopy

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Having a problem identified on a screening test and undergoing subsequent procedures for diagnosis and treatment is frequently associated with high levels of distress (Marteau, 1989). Such distress may be due to anticipation of further medical procedures as well as concern about the outcome. Recent evidence suggests that women experience both general and specific stresses at all stages of the medical process associated with the diagnosis of an abnormal smear following participation in screening for cervical cancer (Posner & Vessey, 1988; Quilliam, 1988).

The aims of the present study were to measure levels of distress in women recommended to have a colposcopy after an abnormal cervical smear, and to examine the factors contributing to the distress. The longer term aim is to use this information to determine how to minimize distress for these patients.

Subjects and methods

The study included 30 women aged between 20 and 53 years (mean 30·7 years) who were attending the Royal Free Hospital for a first colposcopy appointment. This sample size was chosen as the smallest sample size likely to detect a true difference in anxiety. The presenting problems were an abnormal or suspicious looking cervix in three, and various degrees of cervical intraepithelial neoplasia (CIN) in the other 27: CIN I in 16; CIN II in seven and CIN III in four. The mean length of time from first abnormal smear to the present consultation was 18·7 weeks.

Design of the study

The women were recruited at their first colposcopy appointment. Before they saw the doctor they were asked if they would complete a brief questionnaire before and after their consultation. All those approached agreed to participate. The following information was collected before the consultation.

General anxiety. This was measured using a standardized questionnaire (Spielberger *et al.*, 1970), giving a score of between 20 and 80; 35 is the norm for adult women. A 7-point rating of anxiety was also included.

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Table 1. Anxiety ratings (mean (SD)) in women undergoing colposcopy

Test	Anxiety rating (score)†	
	Before consultation	After consultation
General anxiety		
Questionnaire	51·2 (11·8)	—
7-point rating	3·9 (1·8)	2·2 (1·5)*
Specific anxiety		
About colposcopy	4·2 (1 9)	–
About outcome	4·7 (2·0)	–

*paired t-test: $t=3{\cdot}68$; df=27; $P<0{\cdot}001$.

†Anxiety ratings were scored on the Spielberger State-Trait Anxiety Inventory (range 20-80), lower scores denoting lower levels of anxiety or on a 7-point scale ranging from 1 (not at all anxious) to 7 (extremely anxious).

Specific anxieties. These were assessed in the following areas: (i) anxiety about colposcopy, (ii) anxiety about what the doctor may find wrong, and (iii) perceived seriousness of the problem. These anxieties were measured using 7-point rating scales labelled at one end 'not at all' and at the other 'extremely'. Concerns about colposcopy were assessed by asking the women to check which of seven concerns they had experienced before the colposcopy (anticipated pain, anticipated discomfort, being seen naked, feeling embarrassed, being uncertain as to what will happen, the doctor not explaining things, not understanding what the doctor says).

Statistical analysis

The data were analysed using the statistical package for the social sciences, version x (SPSSx). Results were considered significant when the probability of them having occurred by chance alone was ≤5%.

Results

Anxiety levels in this group of women were extremely high, with a mean score of 51·2 (SD11·8), this is higher than anxiety levels in women the night before surgery (Johnston, 1980) and similar to anxiety levels in women following an abnormal result on AFP screening for fetal abnormality (Marteau *et al.*, 1988). These women were as concerned about undergoing colposcopy as they were about what the doctor might find wrong with them (Table 1).

There was no relation between these anxiety scores and the seriousness of the referred problem, the perceived seriousness of problem, parity, or time since referral. However, general anxiety was significantly associated with anxiety about undergoing colposcopy ($r=0{\cdot}62$; $P<0{\cdot}0001$). There was a small but non-significant relation between general anxiety and anxiety about what the doctor might find ($r=0{\cdot}29$; $P<0{\cdot}06$).

The three most frequently cited concerns about colposcopy before the procedure were that is would be painful ($n = 20$), that it would be uncomfortable ($n = 15$); and uncertainty over what would happen during the procedure ($n = 14$). Women who were uncertain about what would happen were significantly more anxious than those without this concern, their mean anxiety scores were 56·2 (SD11·1) *vs* 47·1 (SD11·2) ($t = 2{\cdot}16$; df = 28; $P<0{\cdot}05$); women who were concerned about pain tended to be more anxious than those who were not so concerned, their mean anxiety scores were: 53·8 (SD12·2) *vs* 46·2 (SD9·6) ($t = 1{\cdot}85$; df = 28; $P = 0{\cdot}08$).

Data were obtained for 28 women after their consultations. Overall, the women were significantly less anxious after the consultation than before (Table 1).

Comment

These results demonstrate extremely high levels of distress in this group of women, distress which is more strongly related to anticipation of the procedure than the outcome. Given the three main concerns about colposcopy, it seems likely that providing women with appropriate information about the procedure and levels of pain and discomfort to expect may allay some of their anxieties. There is good evidence from other areas of health care showing the benefits of providing patients with detailed information about their treatments and conditions (Ley, 1988). With waiting lists for colposcopy as long as 6 months in some parts of the country, it is pertinent to consider at which point to intervene: at the colposcopy appointment, when the appointment for colposcopy is made, or as part of the initial preparation for undergoing a smear test.

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Antenatal attendance and fasting of pregnant Muslims during Ramadan

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The fast of Ramadan takes place during the ninth lunar month of the Muslim calendar, so occurring a little earlier each year, and during this time Muslims observe a total fast between the hours of sunrise and sunset. Previous studies have shown that many patients change the way they take prescribed drugs during this time (Aslam & Assad 1986; Aslam & Wilson 1989). Pregnant women and those breastfeeding are excused from fasting but whether this exemption is, in fact, utilized by pregnant Muslim women and the effect that the fast has on antenatal clinic attendance is unknown.

To investigate this question we performed a retrospective analysis to compare the antenatal clinic attendance at Dudley Road Hospital over the fast of Ramadan in 1989 (7 April to 8 May) and a period of similar length outside Ramadan (6 March to 6 April), for both Muslim and non-Muslim women. In addition, 78 consecutive Muslim women, attending the antenatal clinic outside of Ramadan, completed a questionnaire regarding their observance of the fast whilst pregnant and their intention to attend clinic during it.

Results

The total number of clinics and total patient attendance for the two time periods were similar. Non-attendance rates for both Muslim and non-Muslim populations and both time-

Table 1. Attendance during the study period

	Ramadan	Outside-Ramadan
Total number of antenatal clinics	35	37
Total number of Muslim women booked to attend	221	274
Total Muslim non-attenders	30 (14%)	28 (10%)
Total number of non-Muslim women booked to attend	955	1123
Total non-Muslim non-attenders	122 (13%)	141 (12%)

Bracketed percentages indicate non-attendance rate.

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periods are shown in Table 1. There were no statistical differences in these rates for Muslim women over the two time periods (χ^2_2 1·32; $P>0·5$) nor any difference in non-attendance rates between Muslim and non-Muslim women (χ^2_2 0·4; $P>0·5$). Of the 78 Muslim women questioned 64 (82%) reported that they observed the fast and 44 of them (56%) would continue to do so while pregnant. In addition, 41 of the 78 felt that overall, their calorific intake during Ramadan was less than normal. However, only 5 women (6%) would not attend the antenatal clinic during the fast.

Discussion

A recent report has demonstrated the high perinatal mortality rates among Muslim women, especially those of lower social class (Balarajan & Botting 1989) and the Muslim population served by our hospital is probably similar to these national figures. Regular maternal and fetal examination and nutritional advice are two important aspects of antenatal care, especially for underprivileged women. This survey has shown that the fast of Ramadan does not discourage Muslim women from antenatal clinic attendance and that most do observe the fast and probably have a reduced caloric intake during this part of their religious calendar.

Daytime fasting could have serious implications in the management of pregnant diabetic patients and those taking regular oral medication. Since pregnant women are exempt, although they are required to carry over the number of non-fasting days until they can fast, it would seem appropriate to encourage them to avoid fasting, since their health or that of the baby might be affected. General practitioners, and community health personnel should be aware of the practice so that this advice can be provided before the woman becomes pregnant.

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CORRESPONDENCE

Neonatal thyrotrophin and mode of delivery

Dear Sir,

We read with great interest the article by Lao and Panesar (*Br J Obstet Gynaecol* (1989) **96,** 1224–1227) reporting significantly lower umbilical cord plasma thyrotrophin in 91 babies born by caesarean section than in 90 babies born vaginally.

In an unselected series of 91 509 babies in Hamburg, thyrotrophin was estimated at 5 days using the radioimmunologic thyrotrophin neonatal dry spot test of Becton and Dickinson. Standards were calibrated according to the international WHO reference preparation hTSH MRC 68/38 (NIBSG-London).

Of these 91 509 babies 570 had elevated thyrotrophin levels (>20 mIU/l). Nine of the 570 could not be followed up until an unambiguous classification was possible. Of the other 561 babies, 37 showed persisting thyrotrophin elevation and reduced thyroxine levels (<6 μg/dl) or lingual ectopia thyroid on follow-up, thus they fulfilled the criteria for congenital hypothyroidism (German Hypothyroidism Screening Collaborative 1985; New England Congenital Hypothyroidism Collaborative 1984). The other 524 babies had only transient thyrotrophin elevation, thyroxine levels were always normal, thus these were so-called false-positives.

We formed a control group of 561 babies with normal thyrotrophin levels who were matched for sex, year of birth and obstetric department, using a table of random numbers.

Of the 524 babies with transient thyrotrophin elevation 109 had been born by caesarean section (21%, 95% CI 17 to 25%), whereas in the control group of thyrotrophin-normal babies only 56 of 561 (10%, 95% CI 8 to 13%) were born by caesarean section, thus the difference was statistically significant.

Although our methods differ from those used by Lao & Panesar, the findings are in direct conflict. We found birth by caesarean section associated with *elevated* thyrotrophin and Lao and Panesar found an association with *lowered* thyrotrophin. Our findings are in agreement with those reported by Larsson *et al.* (1981) and Engberg *et al.* (1978). If the correct explanation for thyrotrophin elevation in newborn is 'parturition stress' (Walfish *et al.* 1980), why should this stress sometimes be greater in vaginal births and sometimes in abdominal births? In our view these contradictory results show that the pathogenesis of postnatal thyrotrophin elevation still remains unknown.

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Author's reply

Dear Sir,

The difference between our findings (Lao & Panesar 1989) and those described by Drs

Clemens and Neumann, and supported by Engberg *et al.* (1978) and Larsson *et al.* (1981) is probably related to a difference in timing of neonatal blood sampling. These studies all used blood samples collected by filter paper on the fifth postnatal day, whereas our study, as well as that reported by Fukuda (1987), which also showed a higher thyrotrophin concentration in babies born vaginally, used umbilical cord blood.

In general, neonatal serum thyrotrophin concentration increases rapidly for 30 min from the time of birth and then gradually declines over the next few days (Fisher and Odell 1969). It is possible that the neonatal surge in thyrotrophin might be delayed or prolonged in babies born by caesarean section without the stress of labour and vaginal delivery. An alternative explanation or additional factor for the higher thyrotrophin concentration in the 5-day-old babies might be the higher frequency of neonatal complications reported by Larsson *et al.* (1981).

In an unpublished follow-on study we have observed that of 48 consecutive babies with elevated cord serum thyrotrophin concentration (>20 miu/L) only 2 (4.2%) had genuine hypothyroidism. When compared with a group of normal thyrotrophin babies born on the same day who were matched for maternal parity and age, and had thyrotrophin assayed in the same batch, all the babies with transient hyperthyrotrophinaemia had undergone labour (100% *vs* 89·1%, $P<0·03$) and were born vaginally (100% *vs* 76·1%, $P<0·001$). They also had a longer second stage of labour (mean 37, SD 17 min *vs* 26, SD 24 min, $P<0·05$) and a higher frequency of nuchal encirclement of the cord (13% *vs* 2·2%, $P<0·05$). There was no difference in the occurrence of antenatal complications (19·6 *vs* 21·7%), mean gestation at delivery (39·0 weeks *vs* 39.0 weeks), mean birthweight (3190 g *vs* 3150 g), or frequency of low Apgar scores (4·3% in both groups).

Our findings therefore give further support to the hypothesis that parturition stress is the major cause of thyrotrophin surge in the newborn.

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Topical anaesthesia with lidocaine-prilocaine cream for vulval biopsy

Dear Sir,

We read with interest the report by Dr Byrne *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 497-499] describing the use of lidocaine-prilocaine cream for vulval biopsy. They report a mean onset of anaesthesia of the mucosal surface of 16 min (range 11–22 min). We have studied the anaesthetic onset of EMLA cream before cautery or laser treatment of condylomata acuminata located on the vulval mucosa (Ljunghall & Lillieborg 1989, Rylander *et al.* 1990) and in both studies the onset of analgesia was found to be only 5–7 min.

The longer onset time found by Byrne *et al.* (1989) may be explained by an increased local blood flow caused by repetitive probing with a needle at the site to be biopsied, and this would result in an increased systemic absorption of the local anaesthetics and a slower build-up of local tissue concentrations of lidocaine and prilocaine, and hence a longer onset time. Such differences in the duration of dermal analgesia between untested areas and previously tested sites has been observed (Juhlin & Evers 1990).

We tested the presence of analgesia with a forceps pinch in a similar manner, but each pinch was applied at least 1 cm away from any previously tested site, and at the side of the condylomata to be removed. With this method, 10 of 10 women had complete anaesthesia of the mucosa after 5–7 min (Ljunghall & Lillieborg 1989). When EMLA was applied for 5–10 min, the analgesia was satisfactory for thermocautery in 20 of 22 women. In a second study (Rylander *et al* 1990), 60 women were randomized to treatment with EMLA for periods varying from 1 to 75 min. The patients were then given CO_2 laser treatment (parallel group design). The time to the most effective anaesthesia was 4–5 min. In both studies, application times of $\geqslant$15 min resulted in less effective analgesia than shorter application times.

Our results suggest that the most effective degree of anaesthesia is obtained when EMLA is applied for 5–10 min. In contrast to dermal analgesia which increases with application time from 15 to about 120 min (Arendt-Nielsen & Bjerring 1988, Juhlin & Evers 1990), application times >15 min on the vulval mucosa will result in decreased analgesic efficacy. We do agree with Dr Byrne and her colleagues that our patients benefit from the avoidance of painful injections of local anaesthetics, and that EMLA cream is effective for vulval biopsy. In some patients with extensive condylomata the cream may be an alternative to general anaesthesia. The possibility of local anaesthesia for laser treatment of VIN deserves further study, since such treatment may involve deeper tissues than the removal of condylomata.

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The effect of intravascular transfusion for rhesus haemolytic disease on umbilical artery Doppler flow velocity waveforms

Dear Sir,

Hanretty *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 960-963] postulate that there may be a humoral vasodilator affecting vascular tone which is stimulated simply by the process of needling fetal vessels. They also suggest that there is no increase and possibly a decrease in vascular resistance to flow associated with fetal transfusion, as assessed by Doppler velocimetry. A similar paper from Weiner & Anderson (1989) came to similar conclusions.

There is evidence to support the idea of a vasodilatory mechanism operating in the fetal vascular tree which could respond to needling a vessel: a recent review by Lansmann (1988) surveyed the current knowledge of endothelial mechanosensors and their humoral products. It seems likely that the insertion of a needle tip into the lumen of a fetal vessel can produce locally turbulent flow which may be associated with a large rise in shear stress. This could result in the release of several vasoactive substances including endothelium derived relaxing factor (EDRF), histamine and prostacyclin (PGI), all of which cause profound vasodilatation.

On the second point, the explanation for the observed changes in the Doppler time velocity waveform after fetal intravascular transfusion must be examined more critically. Changes in the systolic/diastolic and other indices are not measures of resistance to flow. They are due to many factors which include the massive changes in fetal whole blood viscosity during transfusion (unpublished data), the increased number of scattering particles (red cells) at the end of the transfusion (Yuan & Shung 1988) and the effect of the above mentioned vasoactive compounds. Some of these factors will compete in their effect on the final Doppler waveform.

We are in the process of trying to analyse the changes in the Doppler time velocity waveform resulting from changes in fetal haematocrit although this is proving to be far from easy.

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BOOK REVIEWS

Obstetric Emergencies (Contemporary Issues in Emergency Medicine) edited by Guy I. Benrubi. Churchill Livingstone, New York, Edinburgh, London, 1990. 250 pages with figures and tables. £29.95.

In parts of the USA 25% of pregnant women receive no prenatal care. Ironically, these women are the ones who are most at risk of maternal and perinatal mortality. The emergency department physician will be in the frontline when these patients present with complications during their pregnancies.

This multi-author book was written with the goal of familiarizing emergency department physicians with common obstetric problems that they are likely to encounter. The stated intention of the authors was to reach medical personnel who had no training in obstetrics and gynaecology. On this basis, the chapters assume no prior knowledge and a number include a full summary of the relevant physiological changes in pregnancy.

The diagnosis and management of emergencies commonly associated with maternal mortality, (hypertensive disorders, pulmonary embolism, haemorrhage, infection and ectopic pregnancy), are dealt with comprehensively. There are useful chapters on medical emergencies and drug treatment, as well as on the role of imaging methods in pregnancy emergencies. The management of trauma in pregnancy is reviewed and includes interesting short sections on burns, electrical injuries and postmortem caesarean section.

The chapter on peripartum emergencies is incomplete and some of the advice peculiarly trans-Atlantic. There is, for example, no mention of the diagnosis and management of prolapsed cord. Although there is a full description of vaginal breech delivery, potential difficulties and the manouevres which should be applied when these occur are not covered. The performance of an 'episioproctomy' for shoulder dystocia would not be regarded as first line management in this country.

This book will be valuable for the particular group of doctors for whom it was written but its broad remit and consequent lack of depth make it less useful for the specialist.

Richard Johanson

Operative Gynecologic Endoscopy (Clinical Perspectives in Obstetrics and Gynecology) edited by J. S. Sanfilippo and R. L. Levine. Springer-Verlag, Heidelberg, 1990. 325 pages with figures and tables, DM178.

The aim of this book is to contribute to the education of clinicians and inspire them towards safer and more imaginative applications of endoscopic surgery. Recently, after a prolonged development phase, interest in what can be accomplished through endoscopes has enjoyed exponential growth. This book is therefore both timely and welcome. There is an introductory chapter on the history of endoscopic surgery by the German father of such techniques, Kurt Semm. The remaining 24 contributors are all Americans, but this transatlantic bias is of no disadvantage to the reader and indeed, nicely complements the recent edition of Ballière's Clinical Obstetrics and Gynaecology (September 1989, ed C. Sutton), which concentrates on the European contribution to laparoscopic surgery. There are detailed descriptions on all the established and many of the new gynaecological endoscopic procedures. The book is practical and contains useful information about techniques and instrumentation. It is clearly written and presented with useful but not unduly expensive illustrations and diagrams. Its 325 pages succeed and contain much which is stimulating. I unreservedly recommend this book for all with an interest in this exciting and rapidly developing field.

Ray Garry

The Infertile Couple edited by R. J. Pepperell, Bryan Hudson & Carl Wood. Churchill Livingstone, Edinburgh, 391 pages with figures and tables, £24.95.

This is the second edition of the standard Australian postgraduate text on infertility. Although there is a thin list of the major Australian gynaecologists active in clinical and research work in infertility. The editors express an ambition for their book to be a successor to the American text by Behrman and Kistner. They have succeeded. This is an eminently practical book, written by clinicians for clinicians. It is the vade-mecum for Australian gynaecologists and should be required reading for the MRCOG as it is for the Australian degree. The British candidate will get all he needs for the examination from this book. It is a book to buy, not borrow, and should be in every infertility clinic.

About 60% of the patients who become pregnant while attending an infertility clinic do so without any obvious relevance to their investigation and treatment; a fact for which very little allowance is made in most writing on infertility. One of the strengths of this book is its cool appraisal of various therapies. For the most part the writing is direct and unfussy in the Australian manner; but there are a few exceptions: 'The talent for rapid, efficient reproduction is assumed by society which urges its constituents to use reliable contraception during their time of sexual activity without procreative intent', is not the most illuminating start to a chapter on unexplained infertility.

The shortcomings of this book are trivial and I mention some only to temper my enthusiasm for it. Some critics would find fault with the Archangel Gabriel's rendition of the last Trump; I do not care for the statement that endometrial tuberculosis is common in Scotland. A good deal of water has run under this bridge since Sutherland. The dating is slight for such a rapidly changing field. Perhaps in a future edition GIFT will rate more than one short paragraph.

Arnold Klopper

Books received some of which may be reviewed at a later date

Pregnancy Autoimmunity and Connective Tissue Disorders edited by J. S. Scott and H. A. Bird. Oxford University Press, Oxford, 1990, 345 pages with figures and tables, £40.00

Medically Assisted Conception. An Agenda for Research report of a Study by a Committee of the Institute of Medicine. National Academy Press, Washington DC 1989, 357 pages, £20.75

Prenatal Care: Reaching Mother, Reaching Infants edited by Sarah S. Brown. Committee to Study Outreach for Prenatal Care. Institute of Medicine, National Academy Press, Washington DC, 1988, 254 pages with figures and tables, $19.95

A Clinical Guide to Obstetric Management by Muhammad Anwar Hussain. Hussain Publications, Dhaka, 1989, 176 pages. Taka 125

The Infectious Diseases of the Female Genital Tract Second edition by Richard L. Sweet and Ronald S. Gibbs. Williams and Wilkins, Baltimore, London, 1990, 494 pages with figures and tables. £59.00

Clinical Practice of Gynecology Volume 1 No 2 1989 Human Papillomavirus Infections edited by Barbara Winkler and Ralph M Richart. Elsevier Science Publishing Co, New York, Amsterdam, London, 1990, 259 pages $35.00, Dfl 90

The Baby Challenge. A Handbook on Pregnancy for Women with a Physical Disability by Mukti Jain Campion. Tavistock Routledge, London and New York, 1990, 219 pages, £10.99

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COMMENTARY

Rest in hospital and twin pregnancy

Recent population-based data (Scottish Stillbirth and Neonatal Death Reports, 1988, 1989) show persisting high perinatal mortality in multiple pregnancy (41 per 1000 births, five times the rate in singleton births). Perinatal deaths are predominantly neonatal deaths in very immature babies, or antepartum intrauterine deaths. After excluding deaths due to malformation, 64·3% of deaths are in babies weighing less than 1000 g. As Cole, who compiled the reports, points out, the true picture is even worse than this because very early losses may not be registered as births at all and where one twin dies very early in the pregnancy, the remaining birth will not be registered as a twin birth.

Obstetricians attempting to improve survival rates have often prescribed bed rest in hospital, either routinely or for a large proportion of multiple pregnancies. Fatigued by the extra burden of the uterine contents and the adaptation to multiple pregnancy, women may often choose to rest at home; but what could the obstetrician hope to gain by prescribing rest in hospital? Outcome measures studied have included mean gestation length, proportion of preterm births, mean birthweight, proportion with low birthweight or low birthweight for gestation, perinatal mortality, infant morbidity and maternal pre-eclampsia.

For many years, the only studies attempting to assess bed rest in twin pregnancy were those which compared women who rested with others whose twins were undiagnosed, were diagnosed late, or who refused to comply with advice or were unable to do so. MacGillivray & Campbell (1988) reported on 13 of these studies. Not surprisingly, results were conflicting, but there was a preponderance of better outcomes in the rested group. However, non-compliers are recognized as a group with worse outcomes unrelated to the intervention itself (Coronary Drug Project Research Group, 1980) and similar problems arise with concealed pregnancy or those with late or little antenatal care (Rosenweig & Schultz 1982). Furthermore, if perinatal losses commonly occur before the gestation at which bed rest is usually advocated, as reported by Patel *et al.* (1984), then not being admitted for rest might be a *consequence* of having been delivered very early, rather than preterm delivery being a result of lack of rest. This methodological problem could be resolved by comparing groups of women delivered after (say) 28 weeks, but the potential benefits of any intervention are obviously limited if applied after the major morbidity has occurred. Another source of selection bias is that if obstetricians were selecting for rest the most complicated cases, then the outcomes in the rested group should logically be worse, even if rest had a beneficial effect. These studies do not provide sound evidence for policy determination.

During the last 5 years, the first randomized controlled trials (RCTs) of bed rest have been reported (Hartikainen-Sorri & Jouppila 1984; Saunders *et al.* 1985; Crowther *et al.* 1989). All have included rather small numbers, but have now been subjected to meta analysis, using categorical variables, by Crowther & Chalmers (1989). There was convincing evidence of a reduction in low birthweight, hypertension and pre-eclampsia, but the proportion with preterm delivery was actually increased and there was no improvement in Apgar scores, perinatal mortality or admission to special care baby units. However, Crowther *et al.* (1989) selected for their trial only women with cervical dilatation, who were entered into the study at a mean gestation of 33·3 weeks; Hartikainen-Sorri & Jouppila commenced rest at 29 weeks, and Saunders *et al.* at 32 weeks, and thus the issue of whether earlier rest, prescribed prophylactically, would be more effective, still remains.

This question has been addressed, if not finally answered, by a further trial from Harare (Crowther *et al.* in this issue p 872) and one from Adelaide (Maclennan *et al.* 1990). Both studies are restricted to uncomplicated twin pregnancy. Crowther *et al.* randomized, and commenced bed rest, at 28–29 weeks, and found no prolongation of gestation at delivery, but there was an increase in mean birthweight and birthweight for gestation. However, Maclennan *et al.* (1990), who randomized at 17 weeks and started rest at 26 weeks, found no beneficial effects. Neither study reports any significant effect on perinatal mortality. It is of interest, however, that in Adelaide a number of deaths in the 'treated' group occurred before or just after admission. Would even earlier admission have had a chance of preventing these? In Harare, on the other hand, a number of intrapartum deaths were reported in the control group, perhaps attributable to late intrapartum surveillance. Campbell (1990) reports that the onset of labour is insidious in twin pregnancy, with 33% admitted to the delivery suite at a cervical dilatation of more than 4 cm, and 11% at 8 cm or more.

It does not seem logical at present to prescribe *routine* bed rest or hospital admission for twin pregnancy and it is doubtful whether further randomized controlled trials of this intervention are justified, especially since, at least in Adelaide, it was very unpopular with women. Trials of other prophylactic measures such as cerclage (Grant 1989) and tocolytics (Keirse *et al.* 1989) show no clear benefit, and another trial from Harare (Ashworth *et al.* in this issue p 878) confirms lack of benefit from salbutamol given from 24 weeks onward, though there was a reduction in neonatal respiratory distress.

However, most of the studies described have excluded women with complications such as antepartum haemorrhage, pre-eclampsia, polyhydramnios, previous cerclage or caesarean section. Women with higher multiple pregnancy will be an increasing problem in developed countries with the current practice of assisted reproduction (MRC Working Party on Children Conceived by In-vitro Fertilization, 1990; IVF and GIFT Pregnancies, Australia and New Zealand, 1987, 1988) but have not been the subject of controlled trials of prophylactic measures. Even for complicated singleton pregnancy, the benefits of rest in hospital have not been clearly established (Hepburn 1987; Fraser & Watson, 1989).

Until randomized controlled trials of rest in hospital for complicated twin pregnancy or higher multiple pregnancy are available, prudent obstetricians will wish to discuss with women the need for admission, with or without rest, when complications arise or when geographical problems exist, (such as residence in remote islands without specialist facilities). Since complications such as antepartum haemorrhage or pre-eclampsia occur in a minority of women, even in multiple pregnancy, trials of preventive or therapeutic measures in complicated cases will need to be based in many centres. That such well conducted research has proved possible in Harare should be a stimulus to obstetricians working in the developed world.

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The effects of hospitalization for rest on fetal growth, neonatal morbidity and length of gestation in twin pregnancy

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Abstract

Objective—To test whether a policy of hospitalization for bed rest, from 28–30 weeks gestation until delivery, lengthens the duration of gestation, improves fetal growth and decreases neonatal morbidity in twin pregnancy.
Design—A randomized controlled trial.
Setting—Harare Maternity Hospital, Zimbabwe.
Subjects—118 women with an uncomplicated twin pregnancy between 28 and 30 weeks gestation.
Intervention—Hospitalization for bed rest. Encouraged to rest in bed as much as possible, although voluntary ambulation was allowed.
Main outcome measures—Gestational age at delivery and number of infants delivered preterm (<37 weeks); birthweight and number of small-for-gestational age (SGA) infants; neonatal morbidity was assessed by number of infants requiring admission to the neonatal unit and the length of stay.
Results—There was no effect on duration of gestation or the occurrence of preterm delivery. Mean birthweight was greater in the hospitalized group ($t = -2{\cdot}28$, df 234, $P = 0{\cdot}02$) and there were fewer SGA infants (OR 0·57, 95% CI 0·33–0·96). No differences were found in neonatal morbidity.
Conclusions—Hospitalization for bed rest does not prolong pregnancy but can improve fetal growth, although this was not reflected in improved neonatal morbidity. Whether twin fetal growth can be enhanced similarly in other populations should be investigated.

Although the frequency of twin pregnancies in Western countries is only 1%, over 12% of all early neonatal deaths are associated with multiple pregnancy (Manlan and Scott 1978) and morbidity is high among the survivors (Pearlman and Batton 1988). Over 70% of the perinatal deaths associated with multiple pregnancy occur before 30 weeks gestation (Keith *et al.* 1980, Hawrylyshyn *et al.* 1982), and fetal growth in twins is reduced from 27–30 weeks gestation compared with singletons (McKeown and Record 1952, Williams *et al.* 1982).

In the belief that prolongation of pregnancy or some other improved outcome may result, hospitalization for bed rest in twin pregnancy has been widely used for over 35 years (Russell 1952; Patel *et al.* 1983; Lowry & Stafford 1985). Assessment by randomized studies of a policy of hospitalization for bed rest in uncomplicated twin pregnancy has been limited (Hartikainen-Sorri & Jouppila 1984; Saunders *et al.* 1985;

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MacLennan *et al.* 1990). Analysis of the fetal growth patterns and perinatal mortality in twin pregnancy suggest that any intervention to prolong pregnancy, and/or prevent intrauterine growth retardation to improve fetal outcome, would need to start before 30 weeks gestation. We therefore conducted a randomized controlled trial to examine whether hospitalization for bed rest from 28–30 weeks gestation until delivery favourably affects fetal growth, neonatal morbidity and length of gestation in twin pregnancy.

Subjects and methods

Women with a twin pregnancy between 28 and 30 weeks gestation attending the special multiple pregnancy antenatal clinic at Harare Maternity Hospital, Zimbabwe were considered for entry into the trial, which ran from 1984 to 1986. Women were excluded if they had a cervical suture, hypertension, a caesarean section scar, an antepartum haemorrhage or uncertain gestational age.

Block randomization was used with no stratification and the researchers involved in treatment allocation were not involved in making the randomization schedule. With consent, the next numbered, opaque, sealed study envelope was opened and the women allocated according to the enclosed instructions to hospitalization for bed rest (hospitalized group) or not (control group). Women allocated to the hospitalized group were requested to come into the antenatal ward as soon after recruitment as was convenient. After admission all were encouraged to rest in bed as much as possible although ambulation was allowed The women received a normal hospital diet and antenatal assessments were made weekly. Women allocated to the control group were encouraged to continue their normal activities at home and were seen weekly at the antenatal clinic. They were admitted to the antenatal ward only if complications arose such as hypertension, preterm labour or prelabour rupture of the membranes. The University Research Board gave approval for the study.

The prime measures of the outcome, with frequencies from previous observational data in the study population (Crowther 1987; personal communication) were preterm delivery, defined as <37 completed weeks gestation (incidence 55%), and small-for-gestational age (SGA), defined as a birthweight below the 10th centile of local singleton standards (incidence 35%). It was estimated that a trial size of 100 would have an 80% chance (beta error 0·20) of detecting a statistically significant difference at the 5% level (alpha error 0·05) if the preterm delivery rate was reduced from 55% to 28%. It was recognized a study size of 200 would be necessary to detect a reduction from 35% to 17.5% in the incidence of SGA infants, for the same power and level of significance.

The gestational age assessments (Dubowitz *et al.* 1970) were made by a neonatologist (C.B) who was unaware of the allocated treatment group Dubowitz scoring, which has been validated in African populations (Brueton *et al.* 1973, Singer *et al* 1973; Raghu *et al.* 1981), was used to confirm gestational age at delivery The other primary measures of outcome (birthweight and need for admission to the neonatal unit) were measurements or decisions taken by staff who were unaware of the group to which the mother had been allocated.

Statistical analysis was by Student's *t*-test to compare means, and odds ratios to compare frequencies between groups; the 95% CI of the odds ratio were derived using the method recommended by Katz *et al.* (1978). There were no interim analyses.

Results

Randomization achieved comparability between the two groups in a number of important respects (Table 1). Results were analysed according to allocation at randomization and despite any non-compliance. Non-compliance was rare: four (7%) of the 58 women allocated to the hospitalized group did not attend for hospitalization and a further 11 (19%) women required leave of absence from the hospital for domestic reasons (mean 6·1 days, SD 4·3). Similarly, 22 (37%) of the 60 women in the control group subsequently required antenatal admission to hospital because complications developed but these women are retained in the control group for the analysis. The comparisons made were thus between a policy of recommending routine hospitalization in uncomplicated twin pregnancy and a policy of advising hospitalization only if complications supervened. Of the women admitted, the mean gestations of the hospitalized group at admission was 29·1 weeks (SD 1·2). The mean gestation of the control group at admission was 35·1 weeks (SD 1·8), on

Table 1. Characteristics of the two study groups

	Hospitalized group ($n = 58$)	Control group ($n = 60$)
Age (years)	26·5 (5·7)	26·7 (5·4)
Nulliparae	9	7
Height (cm)	160·2 (8·3)	159·5 (7·5)
Weight at 28 weeks gestation (kg)	68·2 (10·7)	70·0 (8·6)
Previous preterm delivery	5 (8·6%)	6 (10·0%)
Gestation age at entry (weeks)	29·1 (1·2)	29 2 (1·7)

Results are means (SD) or *n* (%) values as appropriate.

average 6 weeks later than the intervention group. The mean length of stay in the hospitalized group was 35·8 days (SD 21·8) and in the control group 1·6 days (SD 4·1). There were no withdrawals and none was lost to follow-up.

Details of pregnancy and fetal outcome are given in Tables 2 and 3. No effects of hospitalization on the length of pregnancy or the occurrence of preterm delivery were detected. However, the mean birthweight of the twins was increased ($t = -2{\cdot}28$, df 234, $P = 0{\cdot}02$) and the risk of giving birth to a SGA infant was reduced (odds ratio 0·57, 95% CI, 0·33–0·96) in the hospitalized group. No differences in neonatal morbidity, as reflected by low Apgar scores (<7) and the need for admission to the neonatal unit, were observed. The data suggest fewer women in the hospitalized group developed hypertension (≥140/90 mmHg) compared with the control group.

There were two stillbirths in the hospitalized group (one normally formed stillbirth and one intrapartum asphyxial death) significantly fewer than the 11 stillbirths in the control group (three normally formed stillbirths and eight intrapartum asphyxial deaths; classified according to Wigglesworth 1980) (OR 0·24 95% CI 0·08–0·74). Two infants died from immaturity in the hospitalized group compared with one in the control group.

Discussion

Twin pregnancy with its associated high mortality and morbidity remains a perinatal challenge. Several interventions besides hospitalization for bed rest have been investigated to decrease the occurrence of preterm birth and SGA infants in twin pregnancy, including prophylactic cervical cerclage (Weekes *et al.* 1977, Sinha *et al.* 1979. Dor *et al.* 1982) and betamimetic agents (Cetrulo and Freeman 1976, Marivate *et al.* 1977, Gummerus and Halonen 1987). In recent overviews of the randomized trials there is no evidence that cervical cerclage (Grant 1989) or betamimetic agents (Keirse *et al.* 1989) are of benefit in twin pregnancy.

Of all these interventions, hospitalization for bed rest has been the most widely practised. Over 39% of women in the Scottish Twin Study (Patel *et al.* 1983) and 44% of women in the Northern Region Twin Study (Lowry and Stafford 1985) with a twin pregnancy were admitted towards the end of the second and beginning of

Table 2. Pregnancy outcome

	Hospitalized group ($n = 58$)	Control group ($n = 60$)		Significance *P* value
Gestation age at delivery (weeks)	36·1 (2·0)	35·9 (2·1)		NS
Recruitment to delivery interval (days)	49·2 (16·6)	49·3 (20·4)		NS
	n (%)	*n* (%)	Odds ratio	(95% CI)
Delivery <37 weeks	36 (62)	40 (67)	0·82	(0·39–1·74)
Delivery <34 weeks	11 (19)	11 (18)	1·04	(0·41–2·62)
Spontaneous labour	57 (98)	56 (93)	3·35	(0·56–19·92)
Caesarean section	8 (14)	12 (20)	0·65	(0·25–1·68)
Hypertension	3 (5)	9 (15)	0·34	(0·10–1·13)
Prelabour rupture of membranes	7 (12)	5 (8)	1·50	(0·46–4·93)
Other complications	7 (12)	12 (20)	0·56	(0·21–1·49)

NS = Not significant
Results are means (SD) or *n* (%) values as appropriate.

Table 3. Fetal outcome

	Hospitalized group (n = 116)	Control group (n = 120)		Significance *P* value
Birthweight (kg)				
Twin I	2·47 (0·49)	2·32 (0·39)		NS
Twin II	2·40 (0·45)	2·28 (0·47)		NS
Both twins	2·43 (0·47)	2·30 (0·43)		0·02
Small-for-gestational age			Odds ratio	(95% CI)
Twin I	14 (24)	26 (43)	0·43	(0·20–0·91)
Twin II	20 (35)	25 (42)	0·74	(0·35–1·55)
Both twins	34 (29)	51 (43)	0·57	(0·33–0·96)
Neonatal Unit				
Admissions	42 (36)	41 (34)	1·09	(0·64–1·86)
Duration of stay (days)	2·6 (6·1)	3·4 (7·1)		NS
Stillbirths	2	11	0·24	(0·08–0·74)
Early neonatal deaths	2	1	2·03	(0·21–19·69)

Results are mean (SD) or *n* (%) values as appropriate

the third trimester for the sole indication of bed rest. Similarly a Canadian survey showed one in three women were offered hospital admission for rest during their twin pregnancy (Zilbert & Gray 1980), as were 80% of women in a French series (Papiernik 1983, Tresmontant *et al.* 1983). Hospitalization is expensive (Powers and Miller 1979) and for the woman and her family is often a disruptive and stressful experience (White and Ritchie 1984).

In spite of its widespread use, to date there have only been four randomized controlled studies of hospitalization for twin pregnancies reported, three in uncomplicated pregnancies when hospitalization started after 29 completed weeks (Hartikainen-Sorri and Jouppila 1984) or after 32 weeks (Saunders *et al.* 1985) or between 26 and 30 weeks (MacLennan *et al.* 1980), and one in pregnancies judged to be at high risk of preterm delivery on the basis of cervical assessment (Crowther *et al.* 1989). We found no evidence of prolongation of pregnancy as a result of bed rest in hospital, in keeping with the previous trials (Hartikainen-Sorri and Jouppila 1984, Saunders *et al.* 1985, Crowther *et al.* 1989, MacLennan *et al.* 1990).

Improved fetal growth was observed in the hospitalized group, an effect also suggested by the results of the previous randomized trial from Harare in uncomplicated twin pregnancies (Saunders *et al.* 1985) but not by the results of the Finnish trial (Hartikainen-Sorri and Jouppila 1984). Favourable increases in uterine blood flow by bed rest (Suonio *et al.* 1976) and decreased physical activity consequent upon hospitalization (Briend 1979) seem more likely to explain the apparently beneficial effects bed rest had on fetal growth than any influence from improved maternal nutrition due to the hospital diet. Only in extreme conditions such as wartime famine has a convincing relation been shown between maternal food intake and birthweight (Stein *et al.* 1975). Studies of nutritional supplementation reveal increases in mean birthweight lower than expected with low protein composition supplements and a consistent decrease in mean birthweight with high protein density supplements (Rush 1989).

Were the hospitalized infants any better off for being heavier? No significant effects on neonatal morbidity as reflected by Apgar scores or admission to and length of stay in the neonatal unit were seen. However, there were fewer stillbirths in the hospitalized group, asphyxial conditions in labour accounting for the excess deaths in the control group.

The beneficial effects on fetal growth observed with hospitalization for bed rest may well have produced infants that were better able to tolerate the asphyxial stress of labour.

The post-hoc observation of a decreased tendency of developing hypertension in the hospitalized group was also reported by Hartikainen-Sorri and Jouppila (1984) and Saunders *et al.* (1985)

Whether twin fetal growth can be similarly enhanced in other populations should be investigated. Until further evidence is available from controlled studies, hospitalization for bed rest in twin pregnancy with the aim of achieving favourable effects on fetal growth should not become routine clinical practice. Selective hospitalization for women at higher than average risk of poor intrauterine growth or with evidence of fetal growth retardation may be appropriate and this needs controlled assessment.

In conclusion, in this urban African population, bed rest in hospital did not prevent preterm delivery but did enhance fetal growth. Whether similar effects occur in other racial groups and what factors are responsible for the increased growth need to be investigated in further research.

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Failure to prevent preterm labour and delivery in twin pregnancy using prophylactic oral salbutamol

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Summary. A double blind, controlled study was performed to see whether the use of prophylactic oral salbutamol would reduce the incidence of preterm labour in twin pregnancy. Of the 144 women studied, 74 took salbutamol and 70 placebo. No difference was found in the length of gestation, birthweight or fetal outcome, although fewer babies suffered from respiratory distress syndrome in the salbutamol group. Women did not experience troublesome side-effects from salbutamol.

Twin pregnancy accounts for almost 10% of the overall perinatal mortality in the Greater Harare Maternity Unit, the major cause of death being immaturity (Crowther 1987).

Attempts have been made to reduce the occurrence of preterm labour in twin pregnancy by bed rest (Saunders *et al.* 1985) and cervical cerclage (Weekes *et al.* 1979) but without success. Prophylactic β-sympathomimetics have been tried in a few controlled trials with conflicting results. These are discussed by Keirse *et al.* (1989).

In view of our local problem of a high perinatal mortality in twins, we decided to conduct a prospective, double blind, randomized controlled trial at Harare Hospital to see whether oral salbutamol would reduce the occurrence of preterm labour and delivery.

Subjects and methods

In 1987, a total of 32 302 women was delivered in the Greater Harare Maternity Unit and of these 470 were twin deliveries. This gives a twin rate of 1 in 68 pregnancies. The Greater Harare Maternity Unit comprises nine municipal clinics, where low risk pregnancies are cared for, and Harare Central Hospital which takes all the high risk cases and acts as a referral unit for problems from those municipal clinics. As soon as a woman is suspected of having a twin pregnancy, she is referred to Harare Hospital.

The trial was conducted over a 14-month period, November 1986 to December 1987. All women booked in the Greater Harare Maternity Unit, with a twin pregnancy confirmed on ultrasound, were referred to the twin clinic where they were cared for by one or more of the three clinical co-authors Women were entered into the trial at their first clinic visit, from 24 weeks gestation onwards but not later than 32 weeks. All the women were African. Duration of gestation was estimated using either certain dates of the last menstrual period, or ultrasound.

Women were excluded from entering the trial if they suffered from diabetes, hypertension, cardiac disease or had had an antepartum haemorrhage. Ethical permission was granted by the

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Department Research Board, and women gave informed consent.

Coding for salbutamol or placebo was computer randomized and the code, A or B, placed in a sealed envelope. The next consecutive envelope was taken as the woman booked. Neither patients nor researchers knew the code. Group A received salbutamol 4 mg, four times a day, whilst group B received an identical looking placebo tablet four times a day.

On entry into the trial, after a full medical and obstetric history had been taken and examination performed, a midwife explained how to take the tablets and the importance of not missing any. An instruction sheet was given to each woman. Women were seen every 2 weeks until 36 weeks, and then weekly. Medication was discontinued at 36 weeks. Labour was induced if the pregnancy reached 40 weeks gestation.

Compliance was estimated by checking how many tablets remained from the 2 week supply and questioning the patient. Enquiry was made as to whether the patient had experienced any side-effects and the pulse was checked at each visit, as well as the usual antenatal observations. If a woman developed one of the exclusion criteria, as a complication during pregnancy, treatment was discontinued. Antenatal admission was reserved for problems arising during pregnancy and women were not electively admitted for bed rest. Treatment was continued during admission, whenever possible, unless there was a specific contra-indication. If a patient was admitted in early preterm labour, she was treated as the duty consultant wished, with intravenous β-sympathomimetics when appropriate.

After delivery, details of gestation, birthweight and fetal outcome were obtained from the notes. The person recording the details did not know the drug code.

Sufficient numbers were recruited prospectively to have an 80% chance of showing a mean difference of 1 week in gestation (Prescott 1980).

The results were analysed using the *t*-test for mean values and odds ratios with 95% confidence intervals (CI). The drug code was broken only after the data had been analysed.

Results

During the 14-month study period, 160 women were recruited, 19 were nulliparous and 141 parous. However, 16 were lost to follow up after having visited the clinic between 1 to 6 times, 6 from the salbutamol group and 10 from the control group. This left a total of 144 women for analysis; 74 women had taken salbutamol and 70 placebo. The two groups were similar for age, parity, history of previous second trimester miscarriage or preterm labour, and gestation at entry (Table 1). The average length of treatment for the salbutamol group was 5·7 weeks (SD 2·8) and 6·2 weeks (SD 3·1) for the placebo group. Only one woman (placebo group) was induced at 40 weeks gestation.

Compliance was satisfactory, with 69% of the women taking all the tablets and 87% women missing no more than 1 day of treatment. There were no statistically significant differences in compliance between the two groups. Sixteen women in the salbutamol group and 11 in the control group missed between 1 and 3 weeks of treatment. This was caused by missing a clinic visit or discontinuation of treatment, erroneously, during hospital admission. This happened in four women in each group. There were no statistically significant differences between the two groups in terms of mean gestation at

Table 1. Characteristics of the two groups

		Salbutamol (n=74)		Placebo (n=70)	
		No	(%)	No	(%)
Parity	0	10	(14)	7	(10)
	1	13	(18)	15	(21)
	2–4	35	(47)	34	(49)
	≥5	16	(22)	14	(20)
Previous second trimester miscarriage or preterm delivery		11	(15)	12	(17)
Age (years) mean (SD)		26·7	(5·3)	27·3	(5·9)
Gestation at entry (weeks) mean (SD)		28·8	(2·4)	28·0	(2·4)

Table 2. Gestation at delivery and birthweight in the two groups

	Salbutamol (n=74)	Placebo (n=70)	Odds ratio (95% CI)
Gestation at delivery (weeks)	35·9 (2·7)	35·1 (3·2)	
No. delivered at <37 weeks	37 (50%)	43 (61%)	0·63 (0·33–1·22)
No. delivered at <32 weeks	4 (5%)	8 (11%)	0·46 (0·14–1·48)
Birthweight (kg)			
Twin I	2·44 (0·53)	2·35 (0·59)	
Twin II	2·39 (0·47)	2·37 (0·60)	
No with birthweight <2·5 kg			
Twin I	39 (53%)	37 (53%)	0·99 (0·52–1·91)
Twin II	41 (55%)	37 (53%)	1·11 (0·58–2·13)

Results are mean (SD) or n (%) as appropriate

delivery, the proportion of women who were delivered preterm (<37 weeks), mean birthweight of the babies, nor the frequency of low birthweight (<2·5 kg) (Table 2).

Of the 288 babies born, 20 died (Table 3). There were seven deaths in the salbutamol group compared with 13 in the control group but this difference was not statistically significant. There were five fresh stillbirths, two in the salbutamol group and three in the control group. One of the stillbirths in the salbutamol group followed a cord prolapse in a breech presentation at 38 weeks gestation, whilst all the others were at <33 weeks gestation.

There was no statistically significant difference in the 5-min Apgar scores between the two groups (Table 3). The rate of admission to the neonatal unit was similar (Table 3), but a statistically significantly higher proportion of babies in the control group required treatment for respiratory distress syndrome (RDS). Respiratory distress was defined as clinically significant if the baby required oxygen therapy from a headbox or ventilator. Five babies died during the neonatal period in the salbutamol group and 10 in the control group. This difference was not statistically significant. All neonatal deaths were babies born at <33 weeks gestation with RDS, apart from one in the salbutamol group whose main cause of death was sepsis. Six women lost both of their babies. There were no congenital abnormalities noted.

Twenty-three women in the salbutamol group were delivered by caesarean section and 13 in

Table 3. Perinatal and neonatal morbidity and mortality in the two groups

	Salbutamol (n=148) No (%)	Placebo (n=140) No. (%)	Odds ratio (95% CI)
Fresh stillbirths	2 (1)	3 (2)	0·63 (0·11–3·68)
Twin I*	2 (3)	1 (1)	1·86 (0·19–18·2)
Twin II*	0 (0)	2 (3)	0·13 (0·01–2·04)
Apgar score <7 at 5 min	7 (5)	11 (8)	0·59 (0·23–1·52)
Admitted to NNU	55 (37)	63 (45)	0·72 (0·45–1·16)
Treated for RDS	5 (3)	13 (9)	0·37 (0·14–0·95)
Neonatal deaths:	5 (3)	10 (7)	0·47 (0·17–1·32)
Twin I*	2 (3)	6 (9)	0·33 (0·08–1·36)
Twin II*	3 (4)	4 (6)	0·70 (0·15–3·18)
Total deaths	7 (5)	13 (13)	0·5 (0·20–1·23)

*n=74 in salbutamol group and 70 in placebo group.
NNU=neonatal unit.
RDS=respiratory distress syndrome.

Table 4. Reason for antenatal admission in the two groups

	Salbutamol (n=74) No (%)	Placebo (n=70) No. (%)	Odds ratio (95% CI)
Hypertension	7 (10)	3 (4)	2·21 (0·62–7·97)
Prelabour rupture of membranes	6 (8)	4 (6)	1·44 (0·40–5·20)
Preterm labour*	0 (0)	2 (3)	0·13 (0·01–2·04)
Investigation fetal well-being	1 (1)	0 (0)	7·00 (0·14–99·9)
Non-specific complaints	14 (19)	10 (14)	1·39 (0·58–3·34)
Total	23 (31)	17 (24)	1·40 (0·68–2·90)

*Treated with an intravenous β-sympathomimetic, hexoprenaline. One woman gave birth 24 h later and the other after 5 days

the placebo-group (OR 1·94, 95% CI 0·91–4·11). There were a greater number of emergency caesarean sections in the salbutamol group (OR 3·57, 95% CI 1·47–8·67). Six women required an emergency caesarean section for cord prolapse in the salbutamol group, whilst this problem did not occur in the control group.

There was one maternal death in the salbutamol group. This woman had a precipitous labour at 33 weeks gestation, at home, and bled heavily. The cause of death was thought to be from postpartum haemorrhage, but no post-mortem examination was performed. She had been taking salbutamol for 12 days.

No women had to have treatment discontinued because of side effects. None complained of palpitations. Three women in the salbutamol group reported some vomiting, compared with six in the control group. Change in pulse rate during treatment was calculated by subtracting the booking pulse rate from the highest recorded when on treatment. The mean (SD) rise was 9·2 (17·9) beats/min in the salbutamol group and 7·6 (19·1) beats/min in the placebo group This difference was not statistically significant.

Twenty-three women were admitted to hospital antenatally in the salbutamol group and 17 in the control group. The reasons for admission are given in Table 4. There were no statistically significant differences between the two groups either in overall admission rates, or indication-specific admission rates. In no case did admission necessitate withdrawal from the trial, but a few women inadvertently missed a week of treatment

Discussion

This prospective, double blind, randomized study showed no difference in the length of gestation, birthweight or fetal outcome following the use of prophylactic salbutamol in twin pregnancy. The only statistically significant difference was that the babies born to women treated with salbutamol were less likely to suffer from respiratory distress syndrome. Our data are consistent with other published controlled trials, as summarized by Keirse *et al.* (1989).

We were only able to recruit 160 women for this trial in spite of the large number of twin deliveries during the study period. This was because the diagnosis tends to be made late in the third trimester and even during labour. Women travel long distances to attend antenatal clinics at Harare Hospital and there is also a high urban to rural migration. This would explain why a few women missed several weeks of treatment and why some women did not give birth at Harare Hospital and were therefore lost from the study. There were equal numbers of women who had missed 1–3 weeks of treatment in the two groups. We did not give longer supplies of salbutamol since the women agreed to come every 2 weeks and it would have made it more difficult to calculate compliance. We did not find that women were troubled by side-effects from long-term salbutamol. There was no statistically significant alteration in pulse rate in those women taking salbutamol. Tolerance to the side-effects of β-sympathomimetics, within a short period, has been reported by Larsson *et al.* (1977).

The interesting suggestion of a protection from RDS is becoming apparent from the studies using β-sympathomimetics in twin pregnancy.

The mechanism of such an effect is difficult to explain, especially as the data from trials of β-mimetics in singleton pregnancy do not suggest such an effect (Keirse *et al.* 1989). Catecholamines are important in the mechanism of adaptation of the fetal lung at birth (Faxelius *et al.* 1983), and animal experiments have shown that maternal infusion of β-sympathomimetic drugs can stimulate these changes (Ekelund *et al.* 1983).

There were no apparent adverse fetal effects noted from therapy. However, one needs to bear in mind the caution of Keirse (1984), that there may be effects on the development of fetal adrenergic receptors with long-term consequences. Hadders-Algra *et al.* (1986) have suggested that exposure to ritodrine might be associated with less optimal functioning at school.

This study adds further weight to the existing evidence that prophylactic β-sympathomimetics do not appear to be useful in preventing preterm labour and delivery. However, it is possible that a useful reduction in the risk of respiratory distress syndrome may result from this treatment. There were 50% fewer neonatal deaths in the salbutamol group and a statistically significant reduction in the numbers of babies requiring treatment for respiratory distress. The available evidence points to the need for a very large trial to test this hypothesis.

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The relative risks of caesarean section (intrapartum and elective) and vaginal delivery: a detailed analysis to exclude the effects of medical disorders and other acute pre-existing physiological disturbances

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Abstract

Objective—To compare maternal mortalities attributable to vaginal delivery, elective caesarean section (CS) and intrapartum CS.

Design—The number of deaths associated with each method of delivery was ascertained among unselected and among low-risk women by detailed retrospective review of the case-notes of women who died after delivery. The frequency of each method of delivery throughout the study period was ascertained from the computer database and enhanced by analysis of the case-notes of unselected groups of women.

Setting—The Peninsula Maternity Services (Cape Town) during the years 1975–1986 inclusive.

Subjects—A total of 108 maternal deaths arising from 263 075 maternities provided accurate information. The relative frequency of vaginal and abdominal delivery was determined from the computer database. The ratio of elective CS to emergency prepartum CS to intrapartum CS was obtained by review of the first 200 operations in the years 1975, 1977, 1979, 1982 and 1984

Main outcome measures—(i) Mortality rates associated with the different methods of delivery in unselected women and in women who were healthy before surgery; (ii) mortality rates apparently attributable to the method of delivery.

Results—The overall relative risk of mortality associated with caesarean section compared with vaginal delivery was 7 decreasing to 5 after the exclusion of women with medical or life-threatening antenatal complications (eg, haemorrhage, hypertension). The relative risk associated with intrapartum compared with elective sections was 2·3 decreasing to 1·4 after the exclusion of women with medical disorders or life-threatening complications. The relative risk of maternal mortality which was apparently attributable to intrapartum compared with elective sections was 1·7. However, the 95% confidence intervals of these values, even from this large data-set, are wide. Nevertheless, these rates are in broad agreement with an approximation derived from the British confidential enquiries into maternal deaths

Conclusion—The attributable relative mortalities of caesarean section compared with vaginal delivery and of intrapartum compared with elective caesarean section are lower than the overall relative mortalities of these modes of delivery and are approximately 5:1 and 1·5.1 respectively. These data are crucially important in the decision to recommend elective caesarean section compared with trial of labour.

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The appropriate use of caesarean section in obstetric practice has been the subject of considerable attention recently (Haynes de Regt *et al.* 1986). The relative maternal mortality attributable to caesarean section and vaginal delivery and the relative mortalities of elective and intrapartum operations are relevant to this debate. The lower the chances that labour will result in vaginal delivery, the less desirable is a policy of trial of vaginal delivery. The failure rate or trial of vaginal delivery at which elective surgery becomes the safer option depends on the relative dangers of elective versus intrapartum operations on the one hand, and caesarean section versus vaginal delivery on the other.

Previous studies have compared the mortalities associated with caesarean section and vaginal delivery. A relatively large number of operative deliveries are carried out in pregnancies in which antenatal complications exist and, thus, overall comparison of mortality rates is a misleading guide to the relative safety of these methods of delivery *per se*. Exclusion of indirect deaths and fortuitous deaths, as defined by the International Classification of Disease and used in the England and Wales Confidential Enquiries into maternal deaths series, does not eliminate bias because acute obstetric emergencies, such as hypertension and haemorrhage, are both indications for operative delivery and serious maternal risks in their own right. Thus, exclusion of cases with pre-existing medical disease is not sufficient to tell us the relative dangers of elective caesarean section or trial of labour in healthy women with, for example, breech presentation, uterine scar or small pelvis. In this paper we compare maternal mortality among women who have neither medical disorders, nor other pre-existing acute physiological disturbances for which urgent operative delivery might be required.

We acknowledge that factors other than the relative mortality rates of caesarean section versus vaginal delivery should also be taken into account in individual decision making.

Subjects and methods

Detailed summaries have been made of all 108 maternal deaths from 1975–1986 inclusive, arising from 263 075 maternities in Peninsula Maternal and Neonatal Service (PMNS) in Cape Town (Van Coeverden de Groot *et al.* 1982). A note was made of the method of delivery, and if this was by caesarean section, it was further noted whether this was an elective operation, an emergency prepartum or an intrapartum procedure. There were no postmortem caesarean sections. If caesarean section was not carried out, a note was made of whether the woman had been delivered vaginally and if not whether she had been in labour.

Deaths were classified according to the ninth revision of the International Classification of Diseases, Injuries and Causes of Death as in the British Confidential Enquiries into Maternal Deaths (Department of Health and Social Security 1986) as incidental (fortuitous, i.e., apparently completely unassociated with pregnancy, e.g. cancer of the stomach), indirect (due to aggravation of an underlying medical condition, e.g. diabetes) or direct (due to obstetric complications). Direct deaths were further classified into those associated with antepartum complications (e.g. hypertension, haemorrhage) that might have been indications for operative delivery in their own right, and those where these factors were absent and death resulted from other factors arising after the onset of labour, e.g. post-partum haemorrhage (with no previous bleeding), infection (peritonitis, septicaemia), pulmonary embolism and anaesthetic complications. In this way we were able to distinguish deaths associated with trial of vaginal delivery from those associated with elective caesarean section and also to confine this comparison to direct deaths in women with no acute physiological disturbance before labour or elective surgery.

As so often happens this information (the numerator) was much easier to obtain reliably than the relative frequency of each method of delivery (the denominator). The number of vaginal deliveries and caesarean sections have been recorded in the annual reports of the PMNS for the entire study period but the incidences of elective, emergency prepartum and intrapartum operations were not recorded before 1982. The computer database classifies caesarean operations as elective or emergency, but the latter were not separated into intrapartum and prepartum procedures. The notes of the first 200 caesarean sections in 1975, 1977, 1979, 1982 and 1984 were, therefore, scrutinized and the indications for surgery categorized as elective, intrapartum or emergency.

Results

There were 263 075 maternities during the period covered in this study and 108 maternal deaths—a rate of 41 per 100 000. This rate has decreased from 0·45 per 1000 (52 deaths in 115 378 maternities) in the first half of the study to 0·38 per 1000 (56 deaths in 147 697 maternities) in the last 6 years.

Five deaths followed elective caesarean section (Table 1) and 38 followed non-elective operations (Table 2). Sixty-five were not associated with surgery (Table 3). Eighteen of the latter women died undelivered before the onset of labour, while the remainder (47) laboured and were delivered; one of these women died in labour and vaginal delivery was then expedited by the ventouse; the baby died in the neonatal period. If only direct deaths are considered and if women who died undelivered before the onset of labour are excluded (Tables 1, 2 and 3) then there were 25 direct deaths following non-elective caesarean section (14 intrapartum and 11 emergency before the onset of labour), four following elective surgery and 27 associated with vaginal delivery (including the woman who died during labour). If, in addition to exclusion of indirect and incidental (fortuitous) deaths, we also exclude women with risk factors before delivery (eg antepartum haemorrhage, hypertension), then there were two deaths after elective caesarean section and seven following non-elective sections, all seven were associated with failed trials of labour. Similarly the number of direct deaths associated with vaginal delivery, excluding acute physiological disturbances drops to 14 (again we include the single woman who died during labour and who was then delivered by instrument). Thus, if we confine our attention to previously healthy women who might be considered for a trial of labour then there were two deaths following elective surgery, seven following intrapartum surgery and 14 following vaginal delivery.

Table 1. Causes of deaths following elective caesarean section and their classification (1977–1986)

Year	Cause	Classification
1986	Myocardial infarction	Indirect
1981	Placenta praevia; haemorrhage	Direct but not due to caesarean section, ie associated with acute physiological disturbance
1979	Infected broad ligament haematoma	Direct caesarean section death
1977*	Pre-eclampsia; failed intubation	Direct caesarean section death but with acute physiological disturbance
	Breech presentation, Amniotic fluid embolism	Direct caesarean section death

*This death was, however, probably *attributable* to caesarean section

In order to work out the relative risks of each method of delivery, however, we need the denominators; the total number of women who were delivered vaginally, after elective surgery and after intrapartum caesarean section (Ideally we need these figures after exclusion of women with serious medical disorders and other risk factors before delivery especially serious antepartum haemorrhage and severe hypertension. These make up a relatively small proportion of non-emergency elective and intrapartum operations and it is impossible to make an accurate and equal adjustment for these factors among the women forming the numerator and denominator groups. We shall, therefore, confine our attention to the overall rates of these three modes of delivery).

The overall caesarean section rate is 12%, and this has remained constant (range 11–13% per year) over the 12 years of this study. There were 31 569 caesarean sections and 231 506 vaginal deliveries. Among the first 200 sections in 1975, 1977, 1979, 1982 and 1984 there were 270 elective and 730 non-elective procedures. Of the latter 652 were intrapartum. The proportion of elective to non-elective procedures was therefore 27 to 73 which can be extrapolated to 8524 and 23 045 elective and non-elective procedures over the study period. The ratio of elective to emergency prepartum to intrapartum procedures was 27 : 8 : 65. This would imply 20 582 intrapartum procedures over the study period.

The maternal mortality rates associated with the different modes of delivery can be calculated from the above data. These mortality rates, excluding women who died undelivered, are shown with the 95% confidence interval in Table 4. The overall mortalities are given together with the mortality rates after exclusion of indirect deaths, and the rates after exclusion of both these deaths and those associated with acute physiological disturbances due to ante-

Table 2. Causes of death following non-elective caesarean section and how they were classified (1975–1986)*

Year	In labour	Indication	Cause of death	Classification
1985	Y	Breech, poor progress	Sepsis	Direct and healthy before surgery (HBS)
	N	Gunshot wound	?Pulmonary embolism	Fortuitous
	Y	Proteinuric hypertension	Sepsis	Direct but acute pre-existing physiological condition† (APPC)
	N	IUGR	Carcinoma of the oesophagus	Fortuitous
	N	Haemorrhage	Sepsis	Direct; APPC
1984	N	Eclampsia	Eclampsia	Direct; APPC
1983	N	Trauma	Trauma	Fortuitous
	Y	Premature twins	Tuberculosis, meningitis	Indirect
	N	Acute abdomen	Primary hepatoma	Indirect
	N	Eclampsia	Eclampsia	Direct, APPC
	Y	Fetal distress	Sepsis	Direct, HBS
1982	Y	Proteinuric hypertension	Pre-eclampsia	Direct; APPC
	Y	Poor progress in labour	Inhalation, patient had proteinuric hypertension	Direct; APPC†
1981	Y	Poor progress	Sepsis	Direct; HBS
	Y	Essential hypertension	Myocardial infarction	Indirect
	Y	Proteinuric hypertension	Cerebral haemorrhage	Direct; APPC
	Y	Rheumatic heart disease	Myocarditis	Indirect
1980	N	Congestive cardiomyopathy	Heart failure	Indirect
	N	Severe pre-eclampsia	Cerebral haemorrhage	Direct; APPC
	N	Maternal septicaemia	Oesophageal cancer	Fortuitous
	Y	Proteinuric hypertension	Cerebral haemorrhage	Direct; APPC
1979	Y	Fetal distress	Pulmonary embolism	Direct; HBS
1978	N	Eclampsia	Cerebral haemorrhage	Direct; APPC
	Y	Hypertension and poor progress	Eclampsia	Direct, APPC
	N	Placental abruption	Not fully determined	Direct; APPC
1977	Y	Fetal distress and poor progress	Known pulmonary hypertension, recurrent pulmonary embolism	Direct; APPC†
	N	Placental abruption	Sepsis	Direct, APPC†
	N	Pre-eclampsia	Status asthmaticus	Indirect
	Y	Poor progress	Septicaemia	Direct; HBS
1976	Y	Fetal distress	Hepatic failure	Indirect
	N	Proteinuric hypertension	Cerebral haemorrhage	Direct; APPC
	Y	Hypertension	Serum hepatitis	Indirect
	N	Eclampsia	Disseminated intravascular coagulation	Direct; APPC
	N	Eclampsia		Direct; APPC
1975	Y	Poor progress in labour	Inhalation	Direct; HBS
	N	Respiratory insufficiency	Kyphoscoliosis and respiratory arrest	Indirect
	Y	Fetal distress embolism	Pulmonary	Direct, HBS
	N	Placental abruption	Sepsis	Direct; APPC†

*There were no deaths in this category in 1986.

†These patients had a pre-existing physiological disturbance but surgical complications were probably the most important cause of death

Table 3. Maternal deaths where caesarean section was not carried out (1975–1986 inclusive)

Year	Delivered	Cause of death	Classification
1986	Y	Cardiac failure (valve disease); died 6 weeks after delivery	Indirect
	Y	Cardiac failure, mitral stenosis	Indirect
	Y	Septicaemia	Direct, healthy before labour (HBL)
	N	Myocardial infarction	Indirect
	Y (SB)	Post-partum haemorrhage	Direct; HBL
	N	Cerebrovascular accident	Indirect
	Y	Pulmonary embolism	Direct Pre-existing physiological complication (APPC)
1985	N	Mitral stenosis; pulmonary oedema	Indirect
	Y (SB)	Placental abruption, adult respiratory distress, disseminated coagulation (DIC)	Direct; APPC
	Y	Status asthmaticus	Indirect
	N	Placental abruption, DIC, hypertension, cerebral haemorrhage	Direct, APPC
	Y	Mitral stenosis	Indirect
	Y	Lymphoma	Fortuitous
	Y	Mitral incompetence, endocarditis	Indirect
	Y	Pulmonary embolism (post-delivery)	Direct; HBL
	N	Pulmonary embolism (antenatal)	Direct, APPC
1984	Y	Disseminated rhabdomyosarcoma	Fortuitous
	Y	Septicaemia	Direct; HBL
	Y	Rupture of uterus (previous caesarean) + pelvic haematoma and sepsis	Direct; HBL
	Y	Hypertension; cerebral haemorrhage	Direct, APPC
1983	N	Late booking, poorly controlled diabetes; cerebral haemorrhage	Indirect
	N	Premature rupture membranes; septicaemia	Direct; APPC
	N	Status asthmaticus	Indirect
	N	Placenta praevia; antepartum haemorrhage	Direct; APPC
	Y	Collapse after normal delivery; presumed pulmonary embolism	Direct; HBL
	Y	Broad ligament haematoma	Direct; HBL
1982	N	Eclampsia and brain haemorrhage	Direct; APPC
	Y	Pulmonary embolism; initially presenting before labour	Direct; APPC
	Y (SB)	Septicaemia secondary to pyelonephritis, presenting initially before delivery	Direct; APPC
	Y	Mitral stenosis—died 5 weeks after delivery	Indirect
1981	N	Placental abruption with cerebral haemorrhage	Direct, APPC
	Y (SB)	Hypertension, cerebral haemorrhage	Direct, APPC
	Y	Hypertension; eclampsia and cerebral oedema	Direct; APPC
	Y (SB)	Peritonitis due to incarcerated diaphragmatic hernia	Fortuitous
	Y (SB)	Hypertension; respiratory and renal failure	Direct; APPC
	Y (SB)	Ruptured uterus (previous C.S adult respiratory distress)	Direct, HBL
	Y	Hypertension manifesting only after delivery, cerebral haemorrhage	Direct; HBL
1980	Y	Acute infective hepatitis (type A)	Indirect
	Y	Placental abruption; shock lung: Eclampsia	Direct; APPC
	N	Massive placental abruption	Direct; APPC
1979	Y	Acute post-partum lupus encephalopathy	Indirect
	N	Acute hypertension complicating mitral and aortic valve disease, acute pulmonary oedema	Indirect
	Y (SB)	Eclampsia with acute cerebral infarction	Direct; APPC

Table 3.—Continued

Year	Delivered	Cause of death	Classification
	Y (SB)	Viral pneumonia	Fortuitous
	Y (SB)	Pneumonia superimposed on tuberculosis	Indirect
	N	Cardiac failure; Eisenmenger's syndrome	Indirect
	Y	Cerebrovascular accident; hypertensive 44-year-old diabetic	Indirect
	N	Status asthmaticus	Indirect
	Y (SB)	Diabetes and urinary infection before delivery, septicaemic post-partum	Direct; APPC (some would classify as indirect)
	Y	Peritonitis septicaemia	Direct; HBL
	Y	Acute eclampsia and hypertensive encephalopathy with no hypertension before labour. Died before delivery and had post-mortem forceps delivery Baby died	Direct, HBL
	Y	Post-partum haemorrhage	Direct, HBL
1978	Y (SB)	Late presentation with ruptured membranes and septicaemia	Direct; APPC
	Y	Leukaemia	Fortuitous
	Y	Subarachnoid and cerebral haemorrhage thought to be secondary to post-partum hypertension	Direct; HBL
1977	Y	Mitral stenosis, pulmonary oedema	Indirect
	Y	Ruptured uterus	Direct; HBL
1976	Y	Pulmonary tuberculosis	Indirect
	N	Undiagnosed phaeochromocytoma of organ of Zuckerkandl· preterm labour treated with a β-sympathomimetic agent	
	Y (SB)	Malignant hypertension, death 5 months after delivery	Indirect
	Y (SB twins)	Placental abruption; shock	Direct, APPC
1975	N	Pulmonary tuberculosis	Indirect
	Y	Coarctation of aorta; cerebrovascular accident	Indirect
	Y (SB)	Malignant hypertension and renal failure; death 6 months after delivery	Indirect
	N	Alveolar cell carcinoma	Fortuitous

?Not clear whether autopsy was performed. Families frequently refused
SB = stillbirth.

natal obstetric factors (haemorrhage; hypertension). Death rates are calculated for vaginal delivery, elective caesarean section and non-elective surgery. Finally deaths associated with emergency prepartum surgery are excluded to show only those who were sectioned after the onset of labour.

Table 5 shows the relative risks and their 95% CI associated with different modes of delivery in subgroups of women. (Technically, the confidence intervals are slightly wider than those presented because the denominators are estimated from a smaller study of 1000 women) Excluding women who died undelivered, the relative risk

Table 4. Death rates (per 100 000) according to method of delivery in women of different risk categories*

Risk group	Vaginal delivery	Caesarean section		
		Elective	All non-elective	Non-elective intrapartum
Overall	20 (15–25)	58 (10–110)	165 (113–217)	108 (66–150)
Exclusion of indirect deaths	12 (7–17)	47 (3– 91)	109 (66–152)	68 (32–104)
Exclusion of indirect deaths and acute antenatal obstetric disturbances	6 (3– 9)	23 (0– 58)	68 (23–103)	34 (11– 59)

*The 95% confidence intervals are given in parenthesis

Table 5. Relative risks of maternal mortality associated with different methods of caesarean section (CS) and vaginal delivery

Group	Mode of delivery		Relative risk (95% CI)
	CS	Vaginal	
	Deaths/Total deliveries	Deaths/Total deliveries	
Overall	43/31564	47/231506	6·7 (4·4– 9·9)
Direct deaths	29/31569	27/231506	7·9 (4·6–13)
Previously healthy women			
Overall	9/31569	14/231506	4·7 (2·0– 9·9)
Intrapartum CS only*	9/29106	14/231506	5·1 (2·2–11·8)
	Non-elective CS	Elective CS	
	Deaths/Total deliveries	Deaths/Total deliveries	
Direct deaths	25/23045	4/8524	2·3 (1·0– 6·6)
Previously healthy women (intrapartum CS only)*	7/20582	2/8524	1·4 (0·3– 6·9)
Attributable deaths (intrapartum CS only)*	12/20582	3/8524	1·7 (0·5– 6·0)

*excluding emergency caesarean section before the onset of labour.

of maternal mortality associated with caesarean section compared with vaginal delivery is almost 7 rising to nearly 8 if we exclude indirect (and fortuitous) deaths. The relative risk of direct death associated with non-elective compared with elective surgery is 2·3. The main purpose of our study was to exclude women having both indirect deaths and acute physiological disturbances. In this case the relative risk of caesarean section and vaginal delivery can be calculated as 4·7. If we exclude emergency prepartum operations from this calculation then the relative risk changes very little to a value of 5·1. If we now compare intrapartum and elective operations in these low risk women, then the relative risk is only 1·4. Some readers might prefer a comparison of deaths attributable to caesarean section rather than associated with low-risk caesarean sections (the former will include some high-risk cases where death was more plausibly ascribable to operative complications than the pre-existing maternal condition). There were three deaths involved with elective sections and 12 with intrapartum sections in this category (Tables 1 and 2) and the relative risks attributable to these modes of delivery remains very similar at 1·7.

Discussion

This is the largest detailed study of maternal deaths with correction for obstetric factors and provides empirical confirmation that these relative risks are diminished when indirect deaths and other acute physiological disturbances are eliminated. Our findings show that the relative mortalities *associated* with caesarean section and vaginal delivery are much greater than the relative *attributable* risks of these methods of delivery *per se*. Furthermore, the relative mortalities associated with intrapartum and elective delivery are reduced when both medical and acute antepartum obstetric complications are excluded. Calculations of the relative safety of planned caesarean section versus trial of vaginal delivery are very sensitive to changes in the relative mortalities of elective and intrapartum surgery (Feldman & Freiman 1985; Bingham & Lilford 1987) Failure to exclude high risk cases in the Commission for Professional Hospital Activities (CPHA) study (US Department of Health and Human Services 1981) led (or misled) Feldman & Freiman (1985) to conclude that 'prophylactic' caesarean section was safer for all women. The importance of these relative risks (elective versus intrapartum surgery) has been under-emphasized, but since the 95% confidence intervals, even in this extensive study, are wide, we recommend that (1) Future maternal mortality series differentiate between deaths associated with elective, emergency prepartum and intrapartum sections and take account both of medical conditions and acute antenatal obstetric emergencies; and (2) prospective computer databases also classify deliveries in this way; the Korner data-set which all British obstetric departments are required to collect does not differentiate between elective and emergency prepartum operations.

Apart from the CPHA study (US DHHS 1981), two other reports contain information on the relative mortalities associated with caesarean section. A report on maternal mortality in Sweden for the years 1973–79 (Moldin *et al.* 1984), employing a correction for medical factors, gave a mortality rate of 0·18 per 1000 for emergency caesarean section and 0·04 per 1000 for elective caesarean section, a ratio of nearly 5:1 in favour of elective caesarean section, although this is based on small numbers and again contains no adjustment for obstetric complications such as antepartum haemorrhage.

The report on maternal mortality in England and Wales (DHSS 1986) gives enough detail to allow correction for medical complications (direct deaths). After excluding medical complications and fortuitous deaths, the risk of maternal mortality for vaginal delivery was 1·2 per 100 000. In terms of direct death, caesarean section is associated with 13 times the mortality of vaginal delivery; higher than the seven-fold risk in this study. Overall, 'emergency' caesarean sections were found to have a three-fold increased mortality over elective sections. If only direct deaths were included, then the mortality rate of emergency operations was six times that of elective surgery. The report contains a breakdown of 'emergency' operations by indication. Half the direct deaths associated with emergency caesarean section occurred in women with obstetric risk factors before delivery (e.g. hypertension, antepartum haemorrhage). If deaths associated with hypertension and antepartum haemorrhage are excluded, then 80% of the remaining deaths followed caesarean sections for poor progress or fetal distress (and therefore intrapartum procedures), while 20% followed surgery for malpresentation or previous caesarean section (and were probably mostly elective). The authors estimate that intrapartum and elective sections are approximately equally common and this would imply that intrapartum surgery is four times as dangerous as elective. No evidence is given for this assumption and data from the Cape Town Population (Van Coeverden de Groot *et al.* 1985), the CPHA data (US DHHS 1981), data from St James' University Hospital, Leeds, and from the present study suggest that the ratio of 2:1, intrapartum to elective surgery is more likely. On this assumption, the relative mortality of intrapartum compared with elective surgery in the British series would be 2, very similar to the relative risk of 1·5 in this study.

Despite the size of our survey, our estimates of relative risk remain imprecise. In addition there are inaccuracies in our calculations of attributable risk. Although our classification of the cause of death in each case is reliable, denominators regarding the relative frequency of each type of caesarean section (elective, emergency-prepartum or intrapartum), are less reliable since. (1) They were derived from a subset of the total number of operative deliveries and, although this was a substantial sample of the total, this must be less precise than a complete survey. However, our method does have the advantage that the type of surgery (elective versus intrapartum versus emergency prepartum) was very carefully ascertained, routine computer coding might be less rigorous; (2) We have not excluded medical factors and acute obstetric emergencies in the denominator figures when we exclude these factors in the numerator. This probably had little effect because such cases form a relatively small proportion of the totals, especially after we have excluded operations carried out for these conditions (emergency prepartum caesarean sections). The relative frequency of acute disturbances would be low among the remainder of elective and intrapartum operations.

Thus, there are no absolutely reliable data on the relative risks attributable to vaginal delivery, elective caesarean section and intrapartum section. Only this study has attempted to allow for pre-existing obstetric risk factors such as hypertension and antepartum haemorrhage Both this study and the British report on maternal mortality (DHSS 1986) provide very imprecise figures, for example, four direct deaths following elective section in our study and nine in the DHSS (1986) report. It could be argued that maternal mortality in healthy women is so low, irrespective of method of delivery, that attention should be focussed on morbidity, ranging from post-operative pain and pyrexia (Hawrrylyshyn *et al.* 1981; Gibbs *et al.* 1978; Donowitz & Wenzel 1980) to hysterectomy. Only two of the eight publications on major maternal morbidity (Nielson & Hökegård 1983; Patek & Larsson 1978;

Aminkia *et al.* 1981; Hibbard 1976; Jones 1976; Richards & Richards 1982; Johnell *et al.* 1976; Kettering & Wolter 1977) separated elective and emergency caesarean sections. Both Nielson & Hökegård (1983) and Patek & Larsson (1978), found major and minor post-operative complications to be more common after emergency than elective caesarean operations by ratios of 6·5:1 and 5·1:1 respectively but these figures are liable to bias by inclusion of obstetric emergencies such as antepartum haemorrhage. In this case there are no data whatever which would allow us to make the corrections which were possible in the case of mortality. Minor morbidity is also more common following intrapartum than elective procedures (Bourgeois *et al.* 1985; Rudd *et al.* 1982; Hagglund *et al.* 1983). Decision-making in obstetrics will also have to take into account fetal mortality and morbidity and also the long-term effects of a uterine scar—features which have been included in the formal analysis of this decision (Bingham & Lilford 1987; Feldman & Freiman 1985).

The choice between elective caesarean section or trial of vaginal delivery may be difficult where the latter has a high failure rate, eg breech delivery or previous section (Collea *et al* 1980; Gimovsky *et al.* 1983; Anderman *et al* 1984; Watson & Benson 1984; Bingham *et al.* 1987; Songane *et al.* 1987; Flamm 1985; Molloy *et al.* 1987; Lavin *et al.* 1982). Bingham and Lilford (1987) estimated the relative risk of intrapartum versus planned section at 3 or 4 to 1 and their decision analysis therefore favoured elective caesarean section in situations where the chances of failure of trial of vaginal delivery exceed 20–30%. The data in this paper suggest that the relative risks of intrapartum versus elective section in previously healthy women are about 2 to 1 and thus lower than suggested previously. The argument for elective surgery in women with a higher than average risk of failure of trial of labour is therefore weakened, while the argument for 'prophylactic' section, is weaker still. Above all, our results demonstrate that attributable risks should be derived from analysis of mortality rates among women with mortality risks similar to those to whom the decision applies.

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Idiopathic thrombocytopenic purpura in pregnancy: A randomized trial on the effect of antenatal low dose corticosteroids on neonatal platelet count

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Abstract

Objective—To determine the efficacy of antenatal low dose oral betamethasone in preventing neonatal thrombocytopenia and/or bleeding in infants of mothers with idiopathic thrombocytopenic purpura (ITP)
Setting—Hospital department of obstetrics and gynaecology, referral centre
Patients—41 pregnancies in 38 women were randomized The results of 13 pregnancies were considered non-assessable The final analysis involved 14 in the betamethasone group and 14 in the non-treatment group All fulfilled the criteria for ITP.
Interventions—The treated group received 1.5 mg betamethasone orally per day, from day 259 till day 273 and 1 mg from day 273 till delivery.
Main outcome measures—Effects of treatment were assessed in terms of maternal platelet counts after the first trimester and neonatal platelet counts at birth and the first week of life and neonatal bleeding episodes.
Results—There were no significant differences in neonatal platelet counts at birth. Two infants in the betamethasone group and one in the untreated group had a severe thrombocytopenia either at birth or during the first week of life ($<50 \times 10^9/l$) Seven infants in the betamethasone group and six in the non-treatment group had a mild thrombocytopenia The overall frequency of neonatal thrombocytopenia was similar: 64% in the betamethasone group and 57% in the untreated group (95% CI of the true difference: −43.5% to +29.5%) There was also no significant difference in neonatal bleeding episodes.
Conclusions—Low-dose betamethasone in pregnant women with ITP does not prevent thrombocytopenia or bleeding in their newborn infants.

Idiopathic thrombocytopenic purpura (ITP) is one of the most commonly occurring autoimmune disorders in pregnancy (Martin *et al.* 1984). It is caused by the occurrence of autoantibodies against platelet membrane glycoproteins (Von dem Borne 1987). The disease is of great concern because active transport of these autoantibodies across the syncytiotrophoblast causes severe thrombocytopenia (platelet count $< 50 \times 10^9/l$) in 30% of newborns, and bleeding in more

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than 10% of newborns (Kelton 1983). Fear of intracranial haemorrhage has generated an increase in use of caesarean section to deliver women with severe ITP (Martin *et al.* 1984; Territo *et al.* 1973; McMillan 1981).

So far, it has been impossible to predict which newborn infants are at risk by investigating the pregnant woman (Kelton 1983). The platelet count in the fetus can be determined both by umbilical cord sampling *in utero* (Forestier *et al.* 1986) and by fetal scalp blood sampling during delivery after the membranes are ruptured (Ayromlooi 1978; Scott *et al.* 1980; Christiaens & Helmerhorst 1987). However, the use of the first technique is restricted to special centres and may not be justified in this disease, and the second method is associated with a false low fetal platelet count in 25–40% of cases (Scott *et al.* 1980: Christiaens & Helmerhorst 1987).

The findings in a retrospective study by Karpatkin *et al.* (1981) suggested that the administration of prednisone to the pregnant woman with ITP had a beneficial effect on the neonatal platelet count.

We therefore designed a prospective randomized trial to investigate the effects of corticosteroids in pregnancies complicated by ITP on neonatal platelet counts and bleeding complications.

Subjects and methods

All pregnant women with ITP were eligible for the study. We excluded any who were already using corticosteroids. The diagnosis of ITP was made on the basis of a thrombocytopenia (maternal platelet count $<150 \times 10^9$/l) on more than one occasion, the presence of a normal or increased number of megakaryocytes in bone marrow, and the absence of other diseases, of splenomegaly, of antinuclear antibodies and of the use of drugs known to induce thrombocytopenia. We included eight women with normal platelet counts in whom the diagnosis of ITP had been made before the current pregnancy and who had had a splenectomy. Antinuclear factor was detected by standard immunofluorescence techniques, using mouse kidney tissue as a substrate.

The women were randomized before 36 weeks gestation according to a computer generated table of random numbers. Those in the treatment group received betamethasone from day 259 of pregnancy till delivery. The dosage of betamethasone was 0·5 mg thrice daily during the first 2 weeks and 0·5 mg twice daily during the third week.

Maternal platelets were monitored throughout the second and third trimester of pregnancy and during the first week after delivery. Neonatal platelet counts were followed for at least the first week of life. All newborn infants were examined and any bleeding events recorded. The paediatricians who assessed the babies were not blind to the treatment received by the mother.

The two primary end points were the occurrence of neonatal thrombocytopenia and the development of neonatal bleeding complications. Any modification of the planned treatment was defined as a discontinuation but was included in the analysis. Women who were delivered before treatment was to be started were excluded from analysis.

Differences in maternal and neonatal platelet count were assessed with the Mann-Whitney *U* test for independent samples. Differences in numbers of thrombocytopenic newborns or newborns with bleeding disorders were analysed with Fisher's exact test. A test result was considered statistically significant at $P<0{\cdot}05$. Assuming a standard deviation in neonatal platelet count as described previously by Karpatkin *et al*, (1981), we estimated that 5, 8 or 20 patients respectively, would be needed in each arm of the study to detect a 4, 3 or 2 fold increase in median neonatal platelet count in the treated group as compared to the non-treated group.

The study was approved by the review board of the University Hospitals of Utrecht and Leiden and all subjects gave informed consent after receiving written information.

Results

During the trial period from March 1984 to March 1987, 64 pregnancies in 59 women from 34 hospitals were offered for study by their physicians. Twenty three of the women were not admitted to the study. 10 were using corticosteroids, seven had a concomitant disease and six refused to participate. The remaining 41 pregnancies in 38 women were randomized for the trial. The results of six pregnancies in the betamethasone group and seven pregnancies in the untreated group were considered non-assessable and were excluded from the final analysis: Seven because investigations after the first tri-

Table 1. Basic characteristics of the study groups

	Betamethasone (n=14)	Untreated (n=14)
Age (years) mean (SD)	29 (5)	29 (6)
Duration of ITP (years) median	3.7	3.2
(range)	(0·12–26·7)	0·04–16·4
No. of women with splenectomy	4	4
No of women with platelet bound autoantibodies	9	6
Maternal platelet count at entry (×10^9/l)		
median	99	95
(range)	(41–453)	(12–300)

mester disclosed secundary thrombocytopenia, three were lost to follow up, two (one in each group) because their attending physician mistakenly altered treatment and one patient because of preterm delivery before the start of treatment.

Twenty eight pregnancies in 26 women were included in the final analysis, 14 in the betamethasone group (12 women) and 14 in the untreated group. The groups did not differ significantly in basic characteristics (Table 1). In eight the diagnosis had been made during pregnancy. All six women with platelet counts >150 × 10^9/l at entry had had splenectomies. The mean duration of treatment with betamethasone was 19·6 days (median 20·5 days). Two women in the untreated group were finally treated with corticosteroids because of low maternal platelet counts. They were considered discontinuations and included in the data analysis.

The maternal platelet counts during the 2nd and 3rd trimester of pregnancy and postpartum are shown in Figure 1. In both groups the maternal platelet counts did not change significantly during the study period. Treatment with betamethasone did not change the platelet count significantly. No side effects were observed.

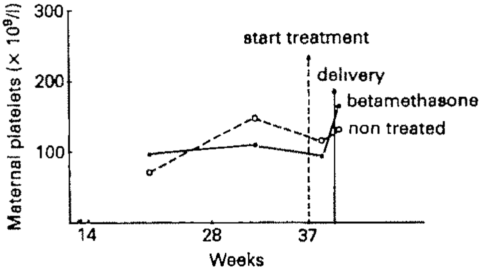

Fig. 1. Maternal platelet counts during pregnancy and postpartum. The median is shown for patients in the betamethasone group (closed symbols) and in the untreated group (open symbols).

Two infants in each group had severe thrombocytopenia (<50 × 10^9/l). In each group, one was detected at birth and one on the 4th day of life. Seven infants in the betamethasone group and six in the untreated group had a mild thrombocytopenia (50–150 × 10^9/l). Of these five and four had mild thrombocytopenia at birth. The 11 other infants had normal platelet counts at birth and throughout the first week of life. The numbers are summarized in Table 2. The overall prevalence of neonatal thrombocytopenia was similar: 64% in the betamethasone group and 57% in the untreated group (95% confidence interval of the true difference: −43.5% to +29.5%). The median neonatal platelet count at birth was 140 × 10^9/l (range 49–298 × 10^9/l) in the betamethasone group and 196 × 10^9/l (range 26–289 × 10^9/l) in the untreated group The median lowest platelet count in the first week of life was 121 (range 15–248 × 10^9/l) and 120 × 10^9/l (range 17–275 × 10^9/l) in the treated and untreated groups, respectively. None of the differences is significant. There was no correlation between maternal and neonatal platelet counts (Figure 2).

The number of babies with bleeding complications was similar in both groups. Three in the betamethasone group had a cephalhaematoma and one also had petechiae. One of these three infants had been born by the aid of forceps. In the untreated group one infant had a small facial haematoma and another had an unspecified scalp haematoma. The latter infant had been born by forceps. All infants with neonatal bleeding, except the two born by forceps, had thrombocytopenia, the lowest counts being 119, 49 and 114 × 10^9/l at birth and 15, 15 and 17 × 10^9/l, respectively.

No side-effects of the treatment were

Table 2. Effect of betamethasone on outcome

	Betamethasone *n*	Untreated *n*
Pregnancies	20	21
Non-assessable	6	7
Infants analysed	14	14
Neonatal platelet count		
Severely depressed		
At birth	1	1
In first week	1	1
Mildly depressed		
At birth	5	4
In first week	2	2
Total no. with		
Low platelet count	9	8
Normal platelet count	5	6*

* Odds ratio treated *vs.* control 1·35 (95% CI 0·3 to 6·2).

observed in any of the newborn infants. The mean birthweight was 3448 g (SD 452) in the betamethasone group and 3203 g (SD 565) in the untreated group.

Discussion

In this prospective randomized study 1·5 mg betamethasone daily, starting on day 259 of pregnancy, did not prevent thrombocytopenia or bleeding in the babies born to women with ITP.

Corticosteroids are the treatment of first choice in the management of ITP (Karpatkin 1985). Dosages of 1–2 mg prednisone/kg are required for an adequate response. Betamethasone is seven times more potent than prednisone and its biological half life is 36–54 h (24–36 h for prednisone). The mechanisms of actions are thought to be inhibition of sequestration of antibody-coated platelets in the mononuclear phagocytic system and suppression of antibody production. *In vivo* studies have shown that betamethasone and dexamethasone cross the human placenta. Cord blood levels of betamethasone are one third of the maternal levels (Ballard *et al.* 1975). Fetal blood levels of prednisolone, the active metabolite of prednisone, are only 10% of the maternal levels (Beitins *et al.* 1972). *In vitro* studies using minced placenta show that betamethasone and dexamethasone are considerably less converted to their inactive 11-ketosteroids than prednisolone (Blanford & Pearson Murphy 1977; Levitz *et al.* 1978). In placental perfusion studies all three steroids were equally converted (Levitz *et al* 1978). Thus betamethasone or dexamethasone are the drugs of choice when fetal treatment is the purpose

Therapeutic dosages for an infant weighing 3400 g are 3·4–6·8 mg prednisone or the equivalent of 0·5–1 mg betamethasone. The average maternal and fetal blood volumes near term are 5200 ml and 340 ml respectively. In order to reach therapeutic levels in the fetus, very high doses (150–300 mg prednisone) would need to be given to the mother.

Previous studies (Karpatkin *et al.* 1981; Logandis *et al.* 1983) suggested that various doses of prednisone, ranging from 10 mg daily to unspecified larger doses, prevented neonatal thrombocytopenia in pregnancies complicated by ITP. In one of these studies (Karpatkin *et al.* 1981) the number of severely thrombocytopenic infants (<50 × 10^9/l) at birth was 5 of 7 (71%) in the untreated group and one of 12 in the treated group, a difference of more than 70%. The design of our trial was different in that patients were randomly allocated to receive treatment or no treatment, furthermore treatment regimens were standardized, and betamethasone was used instead of prednisone for the reasons outlined

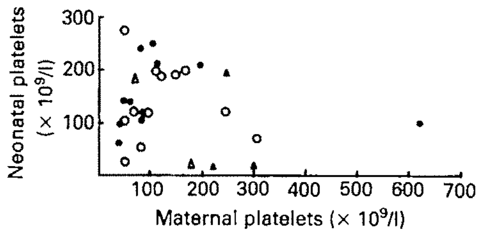

Fig. 2. Relation between maternal platelet counts at delivery and the lowest neonatal platelet counts. All but one of the mothers with platelet counts >150 × 10^9/l at delivery had been splenectomized. The closed symbols represent the betamethasone group, the open symbols the untreated group. The triangles represent infants with bleeding complications. There is no correlation between maternal and neonatal platelet counts

above. The dosages were equivalent to 10 mg prednisone daily. The number of patients in our study should have been sufficient to demonstrate a difference of at least 60% in the occurrence of severe thrombocytopenia at birth, between the two groups.

As could be expected the low dosages of bethametasone used in our study did not affect maternal platelet counts (Karpatkin 1985). The frequency of neonatal thrombocytopenia and of episodes of neonatal bleeding was similar in both groups. The mean neonatal platelet counts did not differ between the groups.

The overall frequency of neonatal thrombocytopenia (<150 × 10^9/l) was 61% (17 out of 28) in our study compared with 46% (48 out of 104) in previous prospective studies or studies of consecutive cases (Karpatkin *et al.* 1981; Cines *et al.* 1982; Scott *et al.* 1983). Severe neonatal thrombocytopenia (<50 × 10^9/l) occurred in 14% of the infants in our study but in 26% in the studies cited above and the frequency of neonatal bleeding in thrombocytopenic infants was equal, namely 10%.

Studies on the relation between maternal and neonatal ITP and the ability of drugs to prevent neonatal disease are thwarted by the disease's heterogenicity. Furthermore, even within maternal subgroups, there is a wide range in neonatal platelet counts. Different activity of certain subclasses of IgG, inactivation of antibodies during passage through the placenta and different degrees of autoantigenic expression on fetal platelets or different sequestration rates of sensitized platelets are possible explanations for the wide range in platelet counts in infants of mothers with ITP. It therefore is important to continue research efforts towards the development of methods to identify the fetus at risk. Once this is possible, it may be useful to study the effect of larger dosages of corticosteroids on neonatal platelet counts in mothers with ITP.

This prospective randomized study in pregnant patients with ITP has shown no benefits from the antenatal use of 1·5 mg betamethasone daily in preventing neonatal thrombocytopenia Other regimens should be the subject of randomized, prospective studies before antenatal corticosteroids are routinely given to the pregnant mother with ITP with as sole aim prevention of neonatal thrombocytopenia.

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Normal early pregnancy: serum hCG levels and vaginal ultrasonography findings

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Summary. Vaginal sonography and determination of serum hCG levels were carried out in 22 healthy pregnant women every 2 to 4 days after the first positive pregnancy test until a living fetus was observed. Gestational age was calculated from the day of ovulation, assessed by LH surge or hCG administration, plus 14 days. A gestational sac of 1–3 mm was detected at a mean (SEM) of 31·2 (0·2) days of gestation (range 30–33 days). The corresponding mean hCG level was 730 iu/l (30) and the range 467–935 iu/l (International Reference Preparation). The yolk sac was detected at a mean of 36·0 (0·2) days, range 34–38 days, at a mean hCG level of 4130 iu/l (370), range 1120–7280 iu/l. Fetal heart motion was visible at a mean of 41·1 (0·3) days, range 39–43 days and the corresponding mean hCG level was 12 050 iu/l (1240), range 5280–22 950, iu/l. The yolk sac and the fetal heart motion were always seen when the sac exceeded 10 and 18 mm in mean diameter, respectively.

The use of the vaginal route for ultrasound scanning has improved accuracy in the diagnosis of early pregnancy complications. The magnification and image resolution offered by the vaginal transducer allow detection of an intrauterine pregnancy earlier and more precisely than with the abdominal transducer (Bernaschek *et al* 1988, Nyberg *et al.* 1988a, Timor-Tritsch *et al.* 1988, Cacciatore *et al.* 1989). A more precise definition of the sonographic criteria for an early gestational sac might further improve this performance.

Reliable determination of gestational age is often impossible in patients with lower abdominal pain and bleeding in the first trimester of pregnancy. The diagnostic value of sonographic findings can be enhanced by reference to serum hCG levels (Romero *et al* 1985, Nyberg *et al.* 1986, Cacciatore *et al.* 1988). Knowledge of the threshold level of hCG above which an intrauterine gestational sac should be seen is particularly important when ectopic pregnancy is suspected. Different thresholds have been reported in recent studies using vaginal sonography (Bernaschek *et al.* 1988, Nyberg *et al* 1988a, Fossum *et al.* 1988, Bree *et al.* 1989) Ectopic pregnancies are associated with hCG levels that are generally lower than in normal pregnancies (Cartwright & DiPietro 1984) and so it is important that this threshold is set to provide as clear a distinction as possible

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The present study correlates serum hCG levels, assessed by a sensitive immunofluorometric assay (Stenman *et al.* 1987), with vaginal ultrasound findings in normal early pregnancy.

Subjects and methods

We studied 22 healthy pregnant women who conceived while attending the infertility clinic of our hospital. In 12 of these women ovulation was induced with clomiphene citrate, alone or in combination with hMG. The other 10 conceived without assistance. The day of ovulation was assessed by detecting the mid cycle urinary luteinizing hormone (LH) surge in 10 women or assumed to occur on the day of hCG administration in 12 women LH was assayed according to the manufacturer's instructions by an immunochemical test with a sensitivity of 30 iu/l (Clearplan, Unipath Ltd, U K.). Gestational age was defined as the number of days after ovulation plus 14 days. Measurement of serum hCG concentration and ultrasound examination were undertaken every 2 to 4 days, starting from the first positive pregnancy test and continuing until a living fetus was observed. The ultrasonographer was not aware of the day of ovulation at the time of each scan. Twenty women had a singleton pregnancy, one a twin and another a triplet pregnancy. All the pregnancies developed normally until delivery. The study was approved by the ethics committee of the hospital.

Serum hCG concentrations were assayed in duplicate on the day of sonography by an immunofluorometric assay (DELFIA Pharmacia Wallac, Turku, Finland) calibrated against the International Reference Preparation (IRP). The data can be converted into the Second International Standard using the equation: 1 iu/l (2nd IS) = 1·8 iu/l (IRP). The assay has a sensitivity of 0·2 iu/l. Because postmenopausal women may have hCG levels up to 9 iu/l a cut off level of 10 iu/l was used to indicate pregnancy (Stenman *et al.* 1987). Unless analysed the same day, the samples were stored at −20°C. The coefficient of variation of the assay at the cut-off point of 10 iu/l was below 8%.

Sonography used Aloka and Hitachi vaginal transducers with emission frequencies of 5·0 and 6·5 MHz, respectively. The women were placed in the lithotomy position and a sterile lubricated condom was placed over the head of the vaginal transducer before insertion. The bladder was empty. The presence of a gestation sac was assumed when an intrauterine fluid collection was found which was either eccentrically located within the endometrium or outlined by a hyperechoic trophoblast rim, or both. Efforts were made to identify the double sac sign due to the different echogenicity between chorion and surrounding decidua (Bradley *et al.* 1982, Cacciatore *et al* 1988, 1989). The average of measurements in three planes was taken as the diameter of the sac

Results

Serum hCG levels and gestational age at which a gestation sac, a yolk sac and fetal heart motion were first detected in the 20 singleton pregnancies are illustrated in Table 1.

The highest hCG level at which the sac was not detected was 475 iu/l while the sac was always seen before serum hCG reached 1000 iu/l. At the time of detection, the gestation sac had a mean diameter of 2·1 mm (range 1–3) (Fig. 1). The double sac sign was detected in 14 pregnancies (70%). In those with twin and triplet pregnancies the sacs were detected at hCG levels of 645 and 1046 iu/l at 31 and 32 days of gestation, respectively (Fig. 2).

A yolk sac was seen when the mean diameter of the sac was 7·0 mm (SD 2·1, range 5–10). At this time the trophoblast rim was about 2 mm thick and sonographically clearly detectable in all pregnancies (Fig. 3).

Fetal heart motion was detected when the mean diameter of the sac was 15·1 mm (SD 1·4,

Table 1. Comparison of earliest sonographic findings with hCG levels and gestational age in 20 normal singleton early pregnancies

Sonographic findings	Serum hCG (iu/l)		Gestational age (days)	
	Mean (SEM)	Range	Mean (SEM)	Range
Intrauterine sac	730 (30)	432–935	31·2 (0 2)	30–33
Yolk sac	4310 (370)	1120–7280	36·0 (0·2)	34–38
Fetal heart beat	12050 (1240)	9280–22950	41·1 (0·3)	39–43

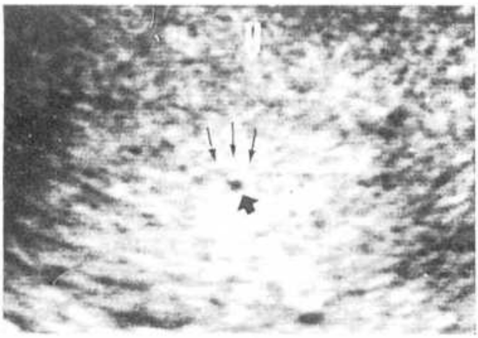

Fig. 1. Transverse scan of the uterus (U) in which a gestation sac of 2 mm (arrow) can be observed in the posterior endometrial layer. The line indicating the cavity is faintly visible (small arrows). The hCG level was 686 iu/l and the gestational age was 31 days.

range 10–18). The smallest embryo in which heart motion could be detected had a length of 2 mm (Fig. 4). There was no difference in the rate of embryo development between pregnancies established after natural or treatment cycles.

Discussion

This longitudinal study shows that vaginal ultrasonogrphy can reliably detect an intrauterine sac by 33 days gestation, a yolk sac by 38 days and fetal echoes with a visible heart motion by 43 days gestation. An intrauterine sac was detected earlier and at lower hCG levels than in some other recent reports. In a longitudinal study Fossum *et al* (1988) detected an intrauterine sac at a mean of 34.8 days, with a corresponding mean hCG level of 1398 iu/l (IRP). Nyberg *et al.* (1988a) reported that an intrauterine sac was reliably detectable when the hCG level exceeded 1800 iu/l (IRP). These diffferences from our results may be due, to some extent, to the study design. The short interval between examinations (2–4 days) may have allowed us to detect sonographic changes earlier than Fossum *et al.* (1988) who used an interval of 3–5 days. In addition, our calculation of the gestational age is based on the time of ovulation plus 14 days rather than the woman's recollection of her last menstrual period. Our results are in agreement with those of Bree *et al.* (1989), who detected a sac in each of 53 women when the hCG level exceeded 1000 iu/l (IRP).

The sonographic criteria used to identify a very early intrauterine sac are also likely to be important. Goldstein *et al.* (1988) reported that in normal pregnancy a sac can be imaged by vaginal sonography when it is >4 mm while the smallest sac detected by Nyberg *et al.* (1988a) had a diameter of 3 mm. We were able to detect correctly an amniotic sac of 1–3 mm. Such an early sac was identified as a fluid collection eccentrically located within the uterine cavity. This is due to the fact that implantation takes place on either side of the endometrium which as a result becomes thicker (Yeh *et al.* 1986, Cacciatore *et al.* 1989). The sac was outlined by an echoic contour due to the trophoblast invasion into the surrounding decidual endometrium. The trophoblast is more echogenic than the surrounding decidua and this finding can help in differentiating a true intrauterine sac from any other intrauterine fluid collection (Bradley *et al.* 1982). Vaginal scanning can identify this sign at a very early stage (de Crespigny *et al.* 1988). However, we have confirmed that the acoustic mis-

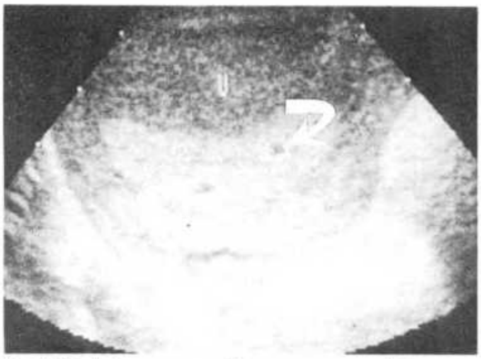

Fig. 2. Triplet pregnancy. Transverse scan of the uterus (U) showing two of the gestation sacs eccentrically located in the anterior and posterior layer of the endometrium. hCG level was 1050 iu/l and gestational age 32 days.

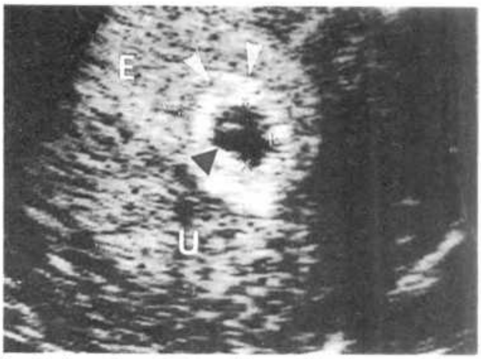

Fig. 3. Imaging of the yolk sac (black arrow) in an intrauterine sac of 6 mm. Also note the decidual-chorionic reaction (white arrows). The hCG level was 5300 iu/l and the gestational age 37 days. U = uterus, E = endometrium.

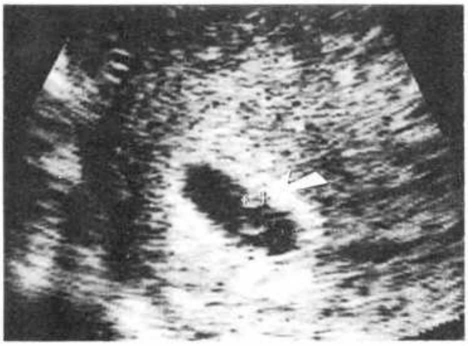

Fig. 4. An embryo of 2 mm in diameter (arrow) is visible close to the yolk sac. The hCG level was 12 500 iu/l and the gestational age 41 days.

match between decidual endometrium and trophoblast is not always detectable before 34 days of gestation (Cacciatore *et al.* 1989). In such cases the amniotic sac should be identified principally on the basis of its location within the endometrium.

One aim of the present study was to define the hCG level above which a sac should be reliably detectable by vaginal sonography. Our results suggest that this threshold should be between 475 iu/l (260 iu/l, 2nd IS), the highest level at which the sac was not seen, and 935 iu/l (510 iu/l, 2nd IS), the highest level at which the sac was seen in a singleton pregnancy. This is in broad agreement with the results of Bernaschek *et al.* (1988), who indicated a range of 300–750 (2nd IS). In our longitudinal study we had two examples of multiple pregnancy that were assessed separately because the hCG levels may be higher than in a singleton pregnancy of the same gestational age (Khazen *et al.* 1986). In the twin pregnancy the sacs were seen at level of 645 iu/l, and in triplet pregnancy at 1050 iu/l. Therefore, we believe that a value of 1000 iu/l might represent a safe threshold above which absence of an intrauterine sac in the vaginal sonogram should be regarded as suspicious of an abnormal pregnancy. The diagnostic value of this threshold in the investigation of early pregnancy complications, and particularly in suspected ectopic pregnancy, needs to be proved by a prospective study.

The yolk sac was detected very early, between 35 and 38 days of gestation. Similar results have been obtained by Warren *et al.* (1989) and by Bree *et al.* (1989). Sonographic identification of this embryonic remnant was not difficult even in relatively small gestation sacs, with an average diameter of 5–10 mm. False positive diagnoses of a yolk sac appear unlikely (Nyberg *et al.* 1988b). Consequently, it can be used as a landmark for corroborating the sonographic diagnosis of an intrauterine sac before a living fetus is detectable.

The fetal heart beat was detected between 39 and 43 days gestation, which represents a relatively small improvement (1–3 days earlier) compared with abdominal sonography (Cadkin & McAlpin 1984). During embryonic development, the two heart tubes fuse and contractions commence only 24–37 days after conception, when the embryo is 2–4 mm (England 1985).

Finally, it is noteworthy that the yolk sac and fetal heart motion were always detected when the average diameter of the gestation sac exceed 10 and 18 mm, respectively. Assessment of embryonic development by vaginal scanning has been found useful in dating early pregnancy (Warren *et al.* 1989) and therefore it is also potentially useful for early diagnosis of miscarriage. We are currently investigating this possibility.

Acknowledgments

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Diagnosis of ectopic pregnancy by vaginal ultrasonography in combination with a discriminatory serum hCG level of 1000 IU/l (IRP)

BRUNO CACCIATORE, ULF-HÅKAN STENMAN, PEKKA YLÖSTALO

Summary. The diagnostic value of vaginal sonography in combination with a discriminatory serum hCG level of 1000 iu/l (International Reference Preparation) was tested prospectively in 200 pregnant women suspected of having an ectopic pregnancy. An ectopic pregnancy was diagnosed in 68 women (34%), a miscarriage in 56 (28%) and a normal pregnancy in 76 (38%). On admission, an intrauterine sac was seen in 89% of the intrauterine pregnancies, but in none of the ectopic pregnancies. Detection of an adnexal mass separate from the ovaries was diagnostic of ectopic pregnancy with a sensitivity of 93%, a specificity of 99%, a positive predictive value of 98% and a negative predictive value of 96%. In 19 patients (9%) the initial sonogram was non-diagnostic and the final diagnosis was obtained after a repeated scan within 6 days. Five of these women had an ectopic pregnancy, 12 a miscarriage and two a normal pregnancy. On admission the hCG level exceeded 1000 iu/l in 77% of all patients and in 67% of those with ectopic pregnancies. In patients with an initial level exceeding 1000 iu/l, an intrauterine sac was found in all the intrauterine pregnancies but in none of the ectopic pregnancies. The use of this threshold in combination with sonographic detection of an adnexal mass was diagnostic of ectopic pregnancy with a sensitivity of 97%, a specificity of 99%, a positive predictive value of 98% and a negative predictive value of 98%.

Early and reliable diagnosis of ectopic pregnancy before tubal rupture is important in preserving future fertility and allowing conservative treatment. High resolution sonography has acquired a strategic role in the diagnostic assessment of suspected ectopic pregnancy, either by demonstrating an intrauterine pregnancy or by detecting an adnexal mass suggestive of ectopic pregnancy (Filly 1987). Development of sensitive and rapid assays allowing quantitative determinations of serum hCG levels (Stenman *et al.* 1987) seems to improve further the diagnostic value of sonographic findings (Romero *et al.* 1985; Nyberg *et al.* 1986; Cacciatore *et al.* 1988). Particularly, determination of a threshold level of serum hCG, above which an intrauterine gestational sac should be seen by ultrasound, may be useful for

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identification of the cases in which absence of the sac should be taken as a diagnostic sign of ectopic pregnancy (Kadar *et al.* 1981; Romero *et al.* 1985).

A number of recent reports have demonstrated that vaginal sonography is more sensitive and specific than abdominal sonography for the diagnosis of ectopic pregnancy (de Crespigny *et al* 1988; Cacciatore *et al.* 1989; Timor-Tritsch *et al.* 1989). In addition, an intrauterine pregnancy can be detected earlier and at lower hCG levels than by abdominal scanning. Nyberg *et al.* (1988) have compared hCG values with vaginal sonographic findings and have suggested a discriminatory hCG level of 1000 iu/l (2nd International Standard), corresponding to 1800 iu/l (International Reference Preparation). This threshold is lower than previously established by abdominal sonography (3600–6000 iu/l, IRP) (Kadar *et al.* 1981; Nyberg *et al.* 1986).

In a longitudinal study in normal early pregnancies we have found that an intrauterine sac is always detectable by vaginal ultrasound when the hCG level exceeds 1000 iu/l (IRP) (Cacciatore *et al.* 1990). The purpose of the present study was to assess prospectively the efficacy of the use of such a discriminatory level in combination with vaginal sonographic findings in the diagnostic assessment of women suspected of having an ectopic pregnancy.

Subjects and methods

Two hundred women with clinical suspicion of ectopic pregnancy (vaginal bleeding and/or abdominal pain) and a positive serum pregnancy test were consecutively recruited between January 1988 and May 1989. Emergency cases, i.e., patients with a clinical picture of acute abdomen requiring immediate surgery, were excluded. The study was approved by the ethics committee of the hospital.

Sonography was performed using vaginal transducers (Aloka, Hitachi), with an emission frequency of 5·0 and 6·5 MHz. For the diagnostic assessment an algorithm based on sonographic findings was used as described previously (Cacciatore *et al.* 1988; 1989). An intrauterine fluid collection was categorized as a gestation sac if it was eccentrically located in the uterine cavity or surrounded by a thickened border as an expression of the decidual chorionic reaction, or both. Lack of evidence for an intrauterine sac at a serum hCG level above 1000 iu/l was taken as diagnostic of ectopic pregnancy. A complex adnexal mass or a gestational sac-like adnexal ring with or without a fetal pole (fetal echoes or yolk sac) were considered diagnostic of ectopic pregnancy if seen to be separate from the ovaries. Pelvic fluid alone, without a concomitant adnexal mass, was not considered diagnostic of ectopic pregnancy.

Serum hCG concentrations were assayed on the day of sonography by an immunofluorometric assay (DELFIA, Pharmacia-Wallac, Turku, Finland), calibrated against the IRP. The data can be converted into the 2nd IS by using the following equation. 1 iu/l (2nd IS) = 1·8 iu/l (IRP). The assay had a sensitivity of 0·2 iu/l. Because postmenopausal women may have hCG levels up to 9 iu/l a cut-off level of 10 iu/l was used to indicate pregnancy (Stenman *et al.* 1987). If repeated determinations were performed, only the first hCG value was considered for the purpose of the study.

An intrauterine pregnancy was classified as normal if ultrasound revealed a live intrauterine fetus and as abnormal if a miscarriage was diagnosed histologically after curettage. The presence of an ectopic pregnancy was confirmed by histological examination of tissue sample obtained during surgery.

The test performance of vaginal sonography and of the discriminatory hCG level was assessed by calculating sensitivity, specificity, positive and negative predictive values (Wald & Cucle, 1989).

Results

Ectopic pregnancy was histologically proven in 68 women (34%), five of whom (7%) had a ruptured tube at surgery. Fifty-six women (28%) had a miscarriage while in 76 women (38%) the outcome was a normal intrauterine pregnancy.

Sonographic findings on admission in comparison to the final outcome are summarized in Table 1. An intrauterine pregnancy was correctly diagnosed by sonography in 89% (117 of 132). An ectopic pregnancy was diagnosed by detecting either a gestational sac-like adnexal ring (Fig 1) or a complex adnexal mass separated from the ovaries (Fig. 2) in 93% (63 of 68). There was one false positive diagnosis of ectopic pregnancy where an adnexal mass was seen by sonography but not confirmed at surgery in a woman who later proved to have a miscarriage. In 9% (19 of 200) of the patients neither an intrauterine sac nor an adnexal mass suggestive of ectopic pregnancy

Table 1. Comparison of initial sonographic findings with the final outcome

Sonographic findings	Final outcome Normal pregnancy	Miscarriage	Ectopic pregnancy
Intrauterine pregnancy (sac and/or fetal pole)	74	43	0
Ectopic pregnancy (adnexal mass or ring)	0	1	63
Non-diagnostic (neither sac nor adnexal mass)	2	12	5
Total	76	56	68

was detected and the initial sonogram was categorized as non-diagnostic. Five of these had an ectopic pregnancy, 12 a miscarriage and two a normal pregnancy. Three ectopic pregnancies were detected on admission because of a hCG level above the threshold. In the other 16 patients the final diagnosis was obtained after a repeated scan, within 6 days.

Serum hCG levels were above 1000 iu/l in 154 of the 200 women (77%); in 45 of the 68 ectopic pregnancies (67%) (Fig. 3) and in 109 of the 132 intrauterine pregnancies (83%). A gestation sac was seen in all intrauterine pregnancies but in none of the ectopic pregnancies when the hCG level exceeded 1000 iu/l (Table 2). An intrauterine fluid collection was actually detected in 9% (6 of 68) of the women with ectopic pregnancy but it was centrally located in the uterine cavity with no visible decidual chorionic reaction. Therefore it was correctly diagnosed as pseudogestational sac. The test performance of vaginal ultrasound findings in relation to the use of discriminatory hCG level is shown in Table 3. The best result was obtained by using as diagnostic criteria of ectopic pregnancy either the detection of an adnexal mass or the absence of an intrauterine sac at an hCG level exceeding 1000 iu/l, or both, with a sensitivity of 97%, a specificity of 99%, a positive predictive value of 98% and a negative predictive value of 98%.

Discussion

The present study was set up to test prospectively the value of a quantitative assay of serum hCG levels in combination with vaginal sonography for the diagnosis of ectopic pregnancy. Our results confirm that vaginal scanning is a very effective tool, allowing direct diagnosis of ectopic pregnancy in 93% on admission and in 100% after a repeated scan (Nyberg *et al.* 1988; Cacciatore *et al.* 1989; Timor-Tritsch *et al.* 1989). This study also demonstrates that absence of an intrauterine sac in the vaginal scan when the hCG level exceeds 1000 iu/l (IRP) is diagnostic of ectopic pregnancy. The combination of this data with the

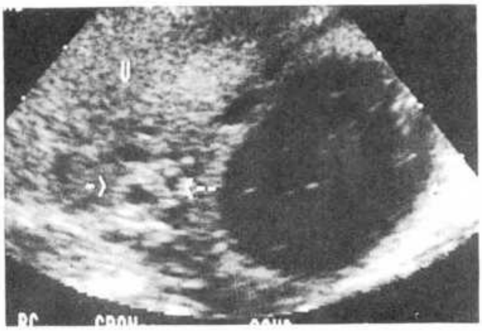

Fig. 1. A small ring with an echoic contour (arrows), suggestive of an ectopic sac can be observed between the uterus (U) and the ovary (OVS) which contains a corpus luteum cyst.

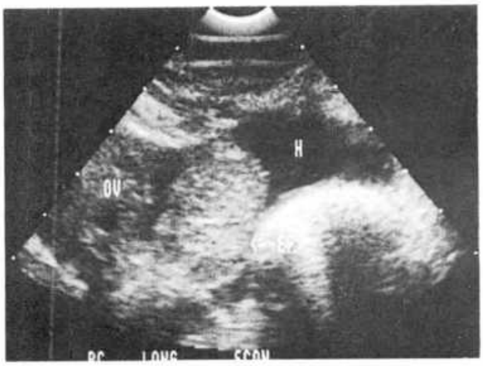

Fig. 2. The ectopic pregnancy appears as a complex mass (EP), separated from the ovary (OV). Pelvic fluid (H) can also be observed.

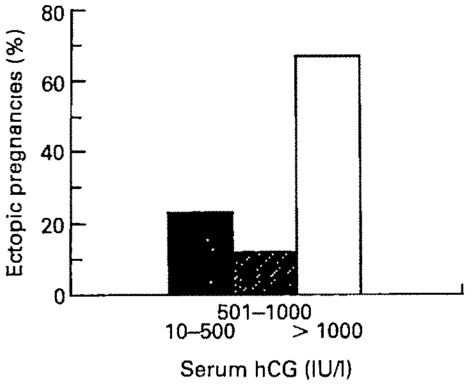

Fig. 3. Distribution of serum hCG levels in women with ectopic pregnancy

sonographic detection of an adnexal mass improved the diagnostic accuracy on admission, confirming that a quantitative assay of serum hCG is valuable in the diagnosis of suspected ectopic pregnancy.

Detection of an adnexal mass by vaginal sonography was a reliable sign suggestive of ectopic pregnancy with a specificity of 99%. This excellent performance is mainly due to the easier identification of the ovaries by vaginal than by abdominal sonography with consequent exclusion of other conditions such as ovarian cysts or endometriomas and direct detection of tubal pathology. However, a reliable sonographic assessment of the adnexa requires an experienced investigator even when vaginal sonography is used Furthermore, some ectopic pregnancies will be missed also by vaginal sonography, mainly when the mass is small or masked by the surrounding bowel loops, as in 7% of our patients on admission. Thus, sometimes only the intrauterine sonogram can be reliably interpretated. The present study confirms that false positive diagnosis of intrauterine pregnancy can be avoided if specific criteria are used for the definition of an intrauterine sac (Mahoney *et al.* 1985; Cacciatore *et al.* 1988). In none of the women with an ectopic pregnancy was an intrauterine sac found and in those where the sonogram showed an intrauterine fluid collection it was correctly identified as a pseudogestational sac. The better image of the endometrium by vaginal scanning improved the detection of an intrauterine sac. However, the uterine cavity looked empty in 13 (11%) of the 132 intrauterine pregnancies, including two normal early pregnancies.

The specificity of intrauterine sonographic findings can be enhanced by comparison with simultaneous serum hCG levels, particularly if a discriminatory level is used, i.e., the hCG level above which absence of an intrauterine sac should be taken as suggestive of ectopic pregnancy (Kadar *et al.* 1981, Romero *et al.* 1985; Nyberg *et al.* 1986). The present prospective study shows that a level of 1000 iu/l (IRP) can be reliably used as discriminatory hCG level. In fact a gestational sac was seen in all the intrauterine pregnancies but in none of the ectopic pregnancies when the hCG exceeded this threshold. On the contrary, a non-diagnostic vaginal sonogram in combination with an hCG level below 1000 iu/l was mostly associated with the presence of an intrauterine pregnancy. Only 14% (2 of 14) of these patients actually had an ectopic pregnancy.

There is a direct correlation between hCG levels and gestational sac size (Nyberg *et al.* 1986; Bernashek *et al.* 1988). Thus, the discriminatory level depends on the ability to identify a very small sac. A threshold of 1000 iu/l would require the ability of detecting a 1–3 mm gestational sac. In our experience this is not difficult, by adopting the eccentric location of the sac or the detection of the decidual-chorionic reaction as sonographic criteria and using sonographic equipment which provides a good magnification and image resolution.

The use of a low discriminatory hCG level is of great clinical value. Romero *et al.* (1985) could detect only 33% of ectopic pregnancies using a threshold of 6000 iu/l, and Nyberg *et al.* (1986) 41% by using a level of 3600 iu/l. More recently, Nyberg *et al.* (1988) could detect 65% (17 of 26) of ectopic pregnancy using a threshold of 1800 iu/l in combination with vaginal sonography. The present prospective study shows that a threshold of 1000 iu/l can increase further this performance,

Table 2. Relation between serum hCG levels and the presence of an intrauterine gestational sac by vaginal sonography

	Final diagnosis					
hCG (iu/l)	Normal pregnancy Sac		Miscarriage Sac		Ectopic pregnancy Sac	
	+	−	+	−	+	−
>1000	72	0	37	0	0	45
<1000	2	2	6	13	0	23

Table 3. Test performance of sonographic findings in relation to the use of a discriminatory hCG level of 1000 iu/l or the diagnosis of ectopic pregnancy

Diagnostic criterion	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
No sac	68/68 (100)	117/132 (89)	68/83 (83)	117/117 (100)
No sac plus hCG>1000 iu/l	45/68 (67)	132/132 (100)	45/45 (100)	110/110 (100)
Adnexal mass	63/68 (93)	131/132 (99)	63/64 (98)	131/136 (96)
Adnexal mass + no sac, hCG>1000 iu/l	66/68 (97)	131/132 (99)	66/67 (98)	131/133 (98)

PPV=positive predictive value NPV=negative predictive value. Sac=intrauterine gestational sac

by detecting 67% of the ectopic pregnancies. The number of ectopic pregnancies with hCG levels above 1000 iu/l was higher than in other reports (Cartwright & DiPietro 1984; Romero *et al.* 1985). Our study design probably contributed to this result. We encouraged prompt referral of patients at a very early stage, which probably facilitated diagnosis of ectopic pregnancy before tubal rupture.

Finally, the combination of adnexal sonographic findings with the use of the discriminatory hCG level improved the diagnostic accuracy. The sensitivity in the diagnosis of ectopic pregnancy on admission increased to 97% because three women with ectopic pregnancy, who did not have a diagnostic vaginal sonogram, could be detected by this criterion. This suggests that, in spite of the high diagnostic accuracy of vaginal sonography, a quantitative assay of serum hCG is valuable in the investigation of suspected ectopic pregnancy.

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Randomized comparison of routine vs highly selective use of Doppler ultrasound and biophysical scoring to investigate high risk pregnancies

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Abstract

Objective—To compare routine versus highly selective use of Doppler ultrasound and biophysical scoring in higher risk pregnancy.

Design—A pragmatic randomized trial.

Setting—St James's University Hospital, Leeds.

Subjects—500 pregnant women at high risk of intrauterine growth retardation or still birth.

Interventions—Regular monitoring with biophysical profile assessment and Doppler velocity waveform recording in umbilical and uteroplacental arteries. Results immediately available to clinicians.

Main outcome measures—Gestational age at delivery, obstetric intervention rates and short-term neonatal morbidity.

Results—Risk factors were distributed very evenly between the 250 patients in the study and control groups respectively. A total of 902 biophysical profile and Doppler assessments were done in the 250 study group patients and only in 12 patients in the control group. In the study group, absent end-diastolic flow was found in only 2·7% of all 902 measurements. A persistently abnormal biophysical score was always associated with absence of end-diastolic flow. The mean gestational age at induction of labour was statistically and clinically similar in the two groups and there was no overall statistically significant difference in intervention rates between the two groups There was a statistically significant lower frequency of depressed 5-min Apgar scores in the study group. Serious neonatal morbidity was also statistically significantly more common in the control group than in the study group.

Conclusions—The use of Doppler ultrasound in higher risk pregnancies does not lead to an increase in iatrogenic preterm delivery. The total rate of positive tests on Doppler ultrasound is very low and persistently abnormal biophysical scores are unlikely to be found in patients where umbilical end-diastolic blood flow is present. Surrogate measures for fetal damage seem to be improved when clinicians have access to Doppler ultrasound assessments.

Much of obstetric care is based on the premise that high risk pregnancies should be monitored by antenatal tests of fetal well-being. Inexpensive Doppler ultrasound equipment became

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available 4 years ago and we acquired this apparatus, along with a conventional ultrasound machine suitable for generating biophysical profile scores. Abnormalities in Doppler waveforms of the uteroplacental and fetal umbilical circulations have been reported to identify fetuses at particularly high risk of mortality and serious morbidity (Rochelson *et al.* 1987; McCowan *et al.* 1987). More recently, abnormal umbilical artery waveforms have been shown to be strongly associated with fetal hypoxia and acidosis (Nicolaides *et al.* 1988; Tyrrell *et al.* 1989). It was postulated that Doppler ultrasound would be a useful addition to our repertoire of tests of antenatal fetal well-being and that timely intervention, on the basis of abnormal Doppler results, might improve obstetrical decision-making (Trudinger *et al.* 1987) and prevent intrauterine death. In addition, because hypoxic cerebral damage may begin before labour (Symonds 1987), and because intrapartum asphyxia is probably more damaging when superimposed on underlying hypoxia, Doppler assessment may lead to intervention that reduces the risk of fetal brain damage. The hypothesis that Doppler is effective in reducing mortality and major morbidity in high risk pregnancy could only be tested with a massive randomized trial (Lilford 1987; De Bono *et al.* 1990), so we have estimated its effect on the occurrence of low Apgar scores and the need for and duration of neonatal special care.

The trial was designed to measure the effect of routine Doppler and biophysical profile testing for all high risk pregnancies as opposed to very selective use of the technology, that is, we compared the intention to use this form of fetal assessment in all high risk pregnancies with the intention not to use it, unless extreme circumstances supervened and early delivery was contemplated. The protocol for the trial placed particular emphasis on the rates of iatrogenic preterm birth, need for neonatal intensive care, and clinical signs of serious neonatal morbidity (hypoxic-ischaemic encephalopathy and major intraventricular haemorrhage) The study was thus designed to answer the pragmatic question: 'should an obstetric department acquire this technology and the necessary staffing for surveillance of all high risk pregnancies?' rather than the question: 'can this technology ever be of use?.'

Subjects and methods

High risk pregnancies were identified by medical staff, either at the booking clinic or when a pregnancy complication occurred antenatally. Only patients from the Leeds Eastern District who were booked for antenatal care at St James's at the request of their general practitioner were considered eligible for trial entry; patients referred from other hospitals were offered Doppler and fetal biophysical investigations if these were considered appropriate, but not as part of the trial.

Risk factors were recognized in 15% of all pregnancies fulfilling the above criteria. We deemed a fetus to be at increased risk of being born small for gestational age (SGA) if intrauterine growth retardation was clinically suspected by a senior obstetrician, or if an ultrasound scan reported a fetal abdominal circumference of $\geqslant 2$ SD below the mean for gestational age. We defined a previous SGA baby as a birthweight < the 10th centile for gestational age, and a previous antepartum haemorrhage (APH) as a haemorrhage that led to an emergency operative delivery. Hypertension was defined as a persistent (>48 h) blood pressure of >140/90 mmHg, and proteinuria was considered significant if a semi-quantitative measurement (Esbach's test) indicated an excess of 0·5 g/24 h in the absence of a urinary tract infection. Serious maternal illness included a wide range of diseases that may influence pregnancy adversely, for example chronic respiratory or cardiac disorders or a renal transplant.

We specifically excluded women with diabetes as there is evidence to suggest that an abnormal umbilical artery Doppler waveform may not predict adverse outcome in this condition (Tyrrell 1988; Landon *et al.* 1989). Multiple pregnancies were excluded because these groups were enrolled in a separate study Smoking, low socioeconomic group and alcohol use were not included as risk factors because although they are associated with poor pregnancy outcome, they would have resulted in almost 70% of our antenatal population being defined as high risk.

All the women in our study were randomized by using a random number sequence contained in sealed, sequentially numbered envelopes Blocking was not used in the randomization schedule. The randomization was performed by the two ultrasonographers involved in the study, neither of whom knew anything about the patients or was involved in their clinical management. It was possible to account for all envelopes and randomization allocations at trial completion.

Randomization resulted in the formation of a routinely investigated and a selectively investigated group. Women in the routinely investigated group had Doppler scans and biophysical profile testing at 28 weeks gestation, or at the time of presentation if risk factors appeared later than this. Thereafter, they had weekly Doppler and fetal biophysical assessments for 3 weeks, followed by fortnightly examinations until delivery. These investigations were made by the ultrasonographers of the fetal assessment laboratory, or by one of us (ST), and were relayed to the clinicians responsible for the woman's care.

The biophysical profile score was modified from that described by Manning *et al.* (1981) by one of us (HNM) and incorporated an ultrasound assessment of amniotic fluid volume and gross fetal limb/body movements, together with response to an external sound stimulus and a non-stressed cardiotocograph (CTG). The method of scoring is shown in Table 1 A score of 8 or 7 was considered normal and an abnormal biophysical score was a score of ≤6. Ultrasound information on amniotic fluid volume and fetal movements was obtained with an Hitachi EUB340 real time scanner using a 3·5 MHz curvilinear transducer. A Sonicaid EM3R cardiotocograph (CTG) recorded the non stressed CTG. External sound stimulation was produced by placing a sound source of 110 dB at 120 Hz on the maternal abdomen adjacent to the fetal head. The sound stimulus comprised four 1-s bursts at 1 s intervals, repeated 2 min later (similar to that described by Birkenfeld *et al.* 1986). Doppler waveforms of the maternal uteroplacental and fetal umbilical arteries were measured and scored as shown in Table 2. Doppler waveforms were recorded and measured with a continuous wave Doppler instrument linked to a fast fourier spectrum analyser with a 100 Hz 'thump' filter (Doptek 9000, Doptek, Chichester, England) A 4 MHz probe was used throughout. All waveforms were recorded for subsequent reference on standard audio tape In each woman both right and left maternal uteroplacental waveforms were recorded as described previously (Schulman *et al.* 1986). The fetal umbilical artery is readily identified, although occasionally (for example in severe oligohydramnios), an offset duplex system linking both real time scanner and Doppler instrument was used to pinpoint the vessel. When recording from this artery, care was taken to ensure that the fetus was neither active nor breathing. For each artery a total of five consecutive waveforms were recorded and measured and the mean value was reported. Due to the availability of established normal ranges we used the resistance index of Pourcelot (RI) to assess the uteroplacental artery waveform and the AB ratio to assess the umbilical artery waveform. An abnormal RI was defined as a value of ≥0·58 (Campbell *et al.* 1986). We defined an abnormal AB ratio in two grades; the less ominous was a value of >95th centile for gestational age (Trudinger *et al.* 1985) which scored 1; a more ominous pattern was absence of the end diastolic component and this scored 0 (Table 2).

In practice, the order of assessment was a real-

Table 1. Reporting method for fetal biophysical profile scoring

Biophysical variable		Score
Fetal movement: no. of gross limb or trunk movements in 10 min		
	2 movements	2
	1 movement	1
	No movement	0
Amniotic fluid volume: depth of fluid pool in vertical axis		
	>2 cm	2
	1–2 cm	1
	<1 cm	0
Sound response: fetal movement or FHR acceleration of 15 b.p.m for 15 s		
	Response to both stimulus	2
	Response to one stimulus	1
	No response	0
Cardiotocography: FHR accelerations of >15 b.p m. for 15 s within 30 min		
	Two reactive episodes	2
	One reactive episode	1
	No reaction	0

FHR=fetal heart rate, b p m.=beats per minute

Table 2. Reporting method for Doppler waveform scores

Variable	Score
Umbilical artery AB ratio	
<95th centile for gestation	2
≥95th centile, end-diastolic flow present	1
Absence of end-diastolic flow	0
Uteroplacental artery resistance index	
<0·58 on both sides of the uterus	2
≥0·58 on one side of the uterus	1
≥0·58 on both sides of the uterus	0

time scan for amniotic fluid volume estimation and fetal movement count, Doppler measurement, sound stimulus and finally CTG. This proved to be the most effective sequence, as initial identification of the fetal umbilical cord and placental position facilitated (but was not essential to) the remaining investigations and after sound stimulation, fetal movements were commonly prolonged, making amniotic fluid assessment and umbilical artery Doppler measurement more difficult. If an abnormal score was recorded the assessment was repeated at more frequent intervals than given above at the discretion of the obstetrician; this could be as frequently as daily, if requested. The obstetricians were fully aware of our earlier study (Tyrrell *et al.* 1989) that had demonstrated a clear association between abnormal fetal umbilical artery Doppler waveforms, especially those with an absent end diastolic component, and antenatal hypoxia and acidosis.

Obstetric investigation in the selectivity investigated group could include growth scans, CTG and kick charts, all as part of either in-patient or out-patient care. Biochemical fetal assessment is not used at St James's Hospital. Clinicians responsible for the care of women in the selectively investigated arm could only obtain Doppler and biophysical assessments on special request, and this happened in only 12 pregnancies After delivery, data were collected on the total number of days of antenatal admission, the rate of induction of labour (by any method), mode of delivery (differentiating between elective and emergency caesarean section), 1 and 5-min Apgar scores, birthweight, and admission to the neonatal unit (NNU). For babies admitted to the NNU, detailed information was obtained on the neonatal course St James's Hospital has a 'transitional' ward for reasonably well low birthweight babies where a high staff to patient ratio allows for many babies, who would otherwise be admitted to the NNU, to be cared for with their mothers. This system ensures that only babies that truly require the services of an intensive care unit are actually admitted to the NNU.

As far as possible we have used end points that are unambiguous. Clearly the trial is not blinded, the women in the routinely investigated group had the information on Doppler and biophysical variables in their notes available for everyone to see. Women in the selectively investigated group simply had a note on the inner face of the case notes stating 'standard care' Although the clinician responsible for the decision to deliver by emergency caesarean section was aware of the patient group allocation, we consider it unlikely that the neonatologist's assessment of fetal condition or the midwife's measurement of the Apgar score were biased by this information.

Statistics

Our main objectives were to measure the effect of the technology on obstetric intervention and neonatal morbidity in these high risk pregnancies. If these tests reduced (or increased) the average number of days on the NNU from 0·2 to 0·15 or 0·25 (assumed SD 0·05), 40 patients in each group would be sufficient, rising to 200 to show a difference of 0·2 to 0·18 (power 80%, P=0·05). To show a difference in the frequency of low Apgar scores from 12% to 5%, 245 patients in each group would be required to reach a P value of 0·05 with a power value of 80% and smaller changes would be measureable with contingency table analysis. The planned trial of 500 patients was therefore sufficient to measure an appreciable decrease in neonatal morbidity and requirements for neonatal intensive care The trial would have a 75% chance of showing a reduction in serious neonatal outcome (probable asphyxiated stillbirth, hypoxic/ischaemic encephalopathy and major (grade 3 or 4) intraventricular haemorrhage) at the 10% significance level. The Mann-Whitney U-test was used to compare durations of antenatal admissions, total 5-min Apgar scores, and gestational age at delivery. To compare rates of induction of labour, caesarean section, SGA-infants and a low 5-min Apgar score, a χ^2-test was used To examine differences between groups in respect of length of stay NNU and ventilation time, a t-test was used Odds ratios were calculated as described by Morris & Garbner (1988).

Results

Comparability of groups (Table 3)

Overall 500 patients were randomly allocated, 250 each to routinely investigated and selectively investigated groups. Some patients were referred with more than one risk factor. There was very little difference in the pattern of risk factors in the two groups. The commonest indications for entry into the study were a diagnosis of intrauterine growth retardation in the current pregnancy, a previous SGA baby, stillbirth or neonatal death of a normally formed baby

Prevalence of abnormal results

A total of 902 biophysical and Doppler assessments were recorded in the 250 patients in the routinely investigated group (mean 3·6, range 1–8) and 580 (65%) showed normal Doppler and biophysical test results. Overall, 886 biophysical assessments were normal (98%) and 12 assessments showed abnormal results both for biophysical variables and Doppler waveforms (either umbilical or utero-placental artery). Four assessments had abnormal biophysical scores but normal Doppler results and all four women had normal biophysical scores on repeat testing the following day. In 60 patients (24%) the umbilical artery waveform had a score of 1 or 0 on at least one occasion and 95 patients (38%) had a score of 1 or 0 in either the umbilical or uteroplacental waveforms or in both on at least one occasion. No patient had a persistently abnormal biophysical score with a normal umbilical artery Doppler waveform, and only 5·9% of all measurements showed severely abnormal umbilical (no end-diastolic component) or uteroplacental waveforms (both sides RI $\geq$0·58). Regardless of uteroplacental waveform measurements, only 2·7% of all investigations showed a severely abnormal (no end-diastolic component) umbilical artery waveform.

Obstetric interventions (Table 4)

There were no differences between the two groups in the length of antenatal stay or rates of induction of labour and elective caesarean section (the data on duration of antenatal stay and induction of labour were obtained retrospectively, and the case notes could not be traced in 15% of the women). There was no statistically significant difference in the rate of elective delivery (either by caesarean section or by induction of labour). Overall, however, the mean gestational age at delivery was lower in the routinely investigated group than in the selectively investigated group, a statistically significant difference which is explained by the difference in the gestational age at spontaneous onset of labour in the two groups.

The gestational age at which labour was induced was slightly earlier in the routinely investigated group (38·1 weeks) than in the selectively investigated group (38·6 weeks) but this difference was not statistically significant (P=0·29, Mann Whitney U-test).

Outcome (Table 5)

In the routinely investigated group there were

Table 3. Indication for referral to the trial in the two investigation groups

Indication	Routine (n=250)	Selective (n=250)
Previous stillbirth or neonatal death	35	29
Previous SGA	59	64
Previous APH	1	4
Serious maternal illness	10	14
Maternal age >40 years	17	14
Hypertension	27	30
Hypertension with proteinuria	7	4
APH in this pregnancy	12	8
IUGR in this pregnancy	90	98

SGA = Small-for-gestational Age;
APH = Antepartum haemorrhage;
IUGR = Intrauterine growth retardation

Table 4. Obstetric characteristics in the two investigation groups

Variable	Routine	Selective		
No. of patients	250	250		
Total no. of tests*	902	22		
Antenatal stay				
(mean no of days/patient)	3·8	3 6	P=0·41	
Gestation (weeks)				
At induction of labour Mean (SD)	38·1 (1·8)	38·6 (1·4)	P=0·29	
At delivery Mean	37·8	38·3	P=<0·01	
Obstetric interventions			Odds ratio	(95% CI)
No. of patients†	230	222		
Induction of labour	69	73	0·87	(0·58–1·30)
Elective section	26	20	1·29	(0·70–2·38)
Total elective interventions	92	91	0·96	(0·66–1·40)

*Doppler waveform measurements and biophysical profile assessments.
†The notes could not be retrieved for all 500 patients and these data were not collected prospectively.

247 live and three still births. Two of these stillbirths were due to multiple congenital abnormalities (one of which was detected at the biophysical assessment). One was a fresh stillbirth in the second stage of labour, the baby was SGA and the Doppler waveforms from the umbilical artery had been abnormal for several weeks. Only five babies with a normal umbilical artery waveform were admitted to the NNU. One of these babies was asphyxiated due to a major placental abruption and one had opiate withdrawal. The other three had little morbidity, none required ventilation, there were no intraventricular haemorrhages and the longest duration of stay on the NNU was 4 days. A total of 98 babies in the routinely investigated group had a birthweight under the 10th centile (corrected for gestational age). Doctors frequently appeared to alter their normal clinical management as a result of the assessment in the routinely investigated group. For example caesarean section was carried out within a week in six of the nine patients with an absence of the end diastolic component in the umbilical artery waveform. In the routinely investigated group as a whole, 13 babies requiring admission to the NNU, and all three stillbirths occurred in the pregnancies associated with an abnormal umbilical artery Doppler waveform (n=41). A total of nine babies were born before 34 weeks gestation, two after spontaneous labour and seven after obstetric intervention.

There were 12 patients in the selectively investigated group for whom biophysical and Doppler

Table 5. Main and secondary outcome variables in the two investigation groups

Outcome	Routine	Selective	Odds ratio	(95% CI)
Main variables				
Livebirth	247	249	–	–
Stillbirth/NND (abnormal baby)	3 (2)	3 (1)	–	–
Elective delivery <34 weeks	7	6	1 17	(0·38–3 60)
5-min Apgar score <7	3	12	0·24	(0·06–0 86)
NNU admissions	18	19	0·94	(0·48–1·84)
Serious neonatal morbidity	1	8	0·12	(0·02–0·98)
Hypoxic encephalopathy	0	5		
Major IVH	0	2		
NND/stillbirth related to hypoxia	1	1		
Secondary variables				
Ventilation time (days)				
Mean (SD)	2·8 (5 3)	2·3 (2·2)	P=0·7	
Duration of stay (days)				
Mean (SD)	26·5 (22·2)	33 6 (21·5)	P=0 34	

NND = Neonatal death; NNU = Neonatal unit; IHV = Intraventricular haemorrhage measurements were specifically requested; these patients were then monitored in the same manner as those in the routinely investigated group.

There was one stillbirth and two neonatal deaths among the 250 patients in the selectively investigated group. The stillbirth was structurally normal and SGA but died at 38 weeks gestation without obvious cause. One neonatal death was due to Edwards' syndrome and the other was due to severe respiratory distress at 28 weeks gestation, the pregnancy had been complicated by severe pre-eclampsia.

There were no statistically significant differences between the two groups in respect of admissions to the NNU (Table 5), but there was a statistically significant difference in the proportion of babies with a low 5-min Apgar score (<7). In the groups overall there were no differences in ventilation time or in duration of antenatal stay.

It is of interest to note that the five babies born after 37 weeks gestation who required admission to the NNU in this trial were all from the selectively investigated group. These admissions were for hypoxic/ischaemic encephalopathy (defined as babies with a combination of neonatal seizures, reduced muscle tone and recurrent apneoic attacks), two of these had the additional complication of meconium aspiration. One of these babies had had a subclinical feto-maternal haemorrhage with an umbilical vein haemoglobin at birth of 3 g/dl. Three babies in the routinely investigated group had postnatal cranial ultrasound scans suggestive of intraventricular haemorrhage (IVH) of grade 1–2. These and all other babies in this group admitted to the NNU were well, with no obvious handicap or disability, at 6-month follow up. Three babies in the selectively investigated group also had cranial ultrasound scan evidence of IVH, one of grade 1, one of grade 3 and one of grade 4. The last two babies now appear to have long-term handicap in that one has hydrocephalus and the other is epileptic with developmental delay at 9 months of age. A third baby from the selectively investigated group, who was admitted to the NNU, has developmental delay at 8 months follow-up. At 14-month follow-up, the baby with a cord haemoglobin of 3 g/dl has developmental delay, with a head circumference below the third centile, and spasticity. The remainder of the group that were admitted to the NNU appear well. There were significantly fewer serious perinatal problems attributable to hypoxia in the routinely investigated group than in the selectively investigated group ($P = 0{\cdot}05$, Table 5).

Discussion

There were no differences between groups in the pattern of risk factors or in the obstetric management variables examined. We found no increase in potentially serious iatrogenic preterm birth at <34 weeks, and in addition there is no evidence that the rate of caesarean sections has increased. Similarly, both the duration of in-patient antenatal stay and the rate of induction of labour, although high overall (reflecting the high risk study population), are not significantly different between the two groups. We can therefore justifiably argue that although obstetricians were aware of a link between abnormal Doppler and biophysical assessments and hypoxia, use of this technology did not increase the risk of obstetric intervention appreciably, and that the evidence strongly suggests that the use of this technology was not harmful in our hands. Significantly more pregnancies in the selectively investigated group had a low 5-min Apgar score <7. Our results therefore suggest that routine biophysical testing with Doppler assessment correctly identifies the small minority of fetuses at risk of hypoxia and alerts the obstetrician to allow for a timely delivery. Indeed, as there was no patient with a persistently abnormal biophysical profile in the presence of a normal umbilical artery waveform, we suggest that Doppler assessment alone in a high risk pregnancy is sufficient, with regular biophysical testing only in those pregnancies complicated by an abnormal umbilical artery waveform. This approach appears to allow for the effective use of Doppler; rarely does Doppler information alone direct the clinician to deliver the pregnancy, but it is an indication for more intense monitoring, allowing for timely delivery without excessive intervention.

Observation of the outcome in patients in the routinely investigated group has confirmed that a normal Doppler waveform in the umbilical artery is strongly linked with a normal neonatal outcome, even in babies who are very SGA (below the 3rd centile). It is assumed that these SGA babies are either constitutionally small or small secondary to other extrinsic factors such as maternal smoking rather than inadequate placental blood flow or function. This is supported by the reported association between increasingly abnormal umbilical artery waveforms and an increasing risk of fetal hypoxia and acidosis (Tyrrell *et al.* 1989).

We now offer Doppler investigation to all high risk pregnancies from 28 weeks gestation as a routine. We have started a randomized trial involving low risk primigravidae where the case for this new technology is not yet made, because the proportion of false positives may be higher, predictive values lower and clinical effect less favourable.

In the meantime, we await the results of other trials of Doppler ultrasound in high-risk pregnancy and look forward to combining those results with ours for meta-analysis (Chalmers *et al.* 1989).

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Hormone implants and tachyphylaxis

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Summary. The serum oestradiol levels of 1388 women treated with hormone implants at a menopause clinic were reviewed in 1988. Thirty-eight (3%) were found to be above 1750 pmol/l. Of these 38 women with supraphysiological oestradiol levels 23 had started therapy for menopausal symptoms and 15 for the premenstrual syndrome (PMS). Of the 23 women treated for menopausal symptoms 11 had a history of psychiatric referral for depression and nine had undergone a surgical menopause. Nine of the 15 women with PMS had a history of psychiatric referral for depressive symptoms. We conclude that the women who attain supraphysiological levels of oestradiol on implant therapy have a high frequency of psychopathology or surgical menopause and may require higher oestradiol levels for adequate control of symptoms.

In recent years the number of women receiving hormone replacement therapy has increased with the recognition of its value in the short-term relief of menopausal symptoms and the longer-term prevention of ischaemic heart disease, strokes and osteoporosis A debate concerning the optimal route of administration and the safety of high oestradiol levels has now developed (Gangar *et al.* 1989). Oestradiol implants, which result in serum oestradiol levels higher than those achieved with other routes of administration, are widely used in some centres. The term 'tachyphylaxis' has been used to describe the return of women to the menopause clinic requesting another implant after just 2 or 3 months because of a return of symptoms. Further implantation after such a short interval results in increasing serum oestradiol levels, because symptoms return before hormone levels reach post-menopausal values and repeated implants even at 6-month intervals tend to be cumulative resulting in increased levels of plasma oestradiol (Cardozo *et al.* 1984).

These women usually complain of the return of psychological symptoms of depression and tiredness rather than vasomotor symptoms but there are no published data concerning the prevalence of 'tachyphylaxis' nor the type of women who develop it. We have studied all the women in our practice who received implant therapy during 1988 to determine the prevalence of supraphysiological levels We reviewed their notes with particular reference to past surgical or psychiatric history

Subjects and methods

The serum oestradiol levels of 1388 women who had been treated by hormone implantation at the Lister Hospital Menopause Clinic were reviewed for the period January to December 1988. Blood tests were performed when the women returned complaining of symptoms and only those who had had two implants or more

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were included in the study. The medical records of the 38 women with serum oestradiol levels >1750 pmol/l were examined to determine the initial diagnosis and any relevant past medical, surgical or psychiatric history. The total duration of therapy and the number and dosage of implants during that time was assessed to determine the mean frequency of implantation.

Implants were inserted as an outpatient procedure as described by Thom & Studd (1980). The starting dose for control of menopausal symptoms was 50 or 75 mg and the dose used for women with the premenstrual syndrome (PMS) or a major depressive component of the symptoms was 75 or 100 mg. Subsequent implantation was performed at the return of symptoms, usually at 6 months, when the dose would generally be reduced to 50 or 25 mg oestradiol. All women with a uterus received cyclical progestogens for the first 7–13 days of each calendar month (Sturdee *et al.* 1978; Studd & Thom 1981).

Results

The mean serum oestradiol level of the 1388 women attending the clinic in 1988 was 767 pmol/l (range 78–2925 pmol/l), 66% had serum oestradiol levels <1000 pmol/l and 3% (38 women) had levels >1750 pmol/l (Fig 1). Table 1 lists the clinical data for these 38 women with supraphysiological oestradiol levels, 15 of them started therapy for PMS and the other 23 for menopausal symptoms.

The 15 women with PMS had a mean serum oestradiol of 2209 pmol/l (range 1760–2820 pmol/l). Their mean age at the start of treatment was 40 years (range 34–54) and the mean duration of therapy was 5·5 years (range 1–12). Nine women (60%) had consulted a psychiatrist for depression before or during therapy.

The 23 menopausal women had a mean serum oestradiol of 2015 pmol/l (range 1785–2925 pmol/l). Their mean age was 46 years (range 29–58) and the mean duration of therapy was 4·5 years (range 1–10) Eleven of these women (48%) had consulted a psychiatrist with depressive symptoms before or during therapy. Nine other women (39%) had undergone a surgical menopause at a mean age of 36·1 years (range 29–50) and none of these gave a psychiatric history. The three remaining women with supraphysiological oestradiol levels underwent a spontaneous menopause and had no psychiatric history.

Discussion

Our data show that high serum oestradiol levels with the use of oestradiol implants is not a common event, occurring in only 3% of 1388 patients. A level of 1750 pmol/l was chosen as the upper limit of the physiological range as this had been shown to be the highest level reached in the menstrual cycle of normal women at the time of the pre-ovulatory surge (Diczfalusy & Landgren 1981). These women had repeat implants inserted on average every 4 months although 6 months is the recommended interval for 50 or 75 mg oestradiol implants (British National Formulary 1989). The fact that these problem women return to the clinic more frequently may result in an observational bias making tachyphylaxis appear more common than it is. We have noted previously the return of climacteric symptoms before plasma hormone profiles returned to pretreatment levels, nevertheless, we found that these symptoms improved with another implant but not with a placebo (Cardozo *et al.* 1984, Brincat *et al.* 1984). This results in a tendency for plasma oestrogen levels to increase in the same manner as when women increase their dose of transdermal oestrogen by self-medication.

A psychiatric history severe enough to warrant referral to a psychiatrist either before or during therapy was present in 20 of the 38 women (52%) with supraphysiological oestradiol levels. The value of implant therapy in women with climacteric depression has been reported previously from this clinic by Montgomery *et al.* (1987) and further unpublished results show that this improvement is maintained after 2 years of therapy

Severe clinical depression occurs with normal oestradiol levels in PMS. Increasing the oestradiol levels with oestradiol implants (Magos *et al.* 1986) or transdermal oestradiol patches (Watson *et al.* 1989) results in a significant improvement in depressive symptoms. These women with severe PMS are free of depression during subsequent pregnancies when serum oestradiol levels are vastly greater than the levels achieved with percutaneous oestradiol therapy. These women may need higher oestradiol levels to control their symptoms and it is clear that many with

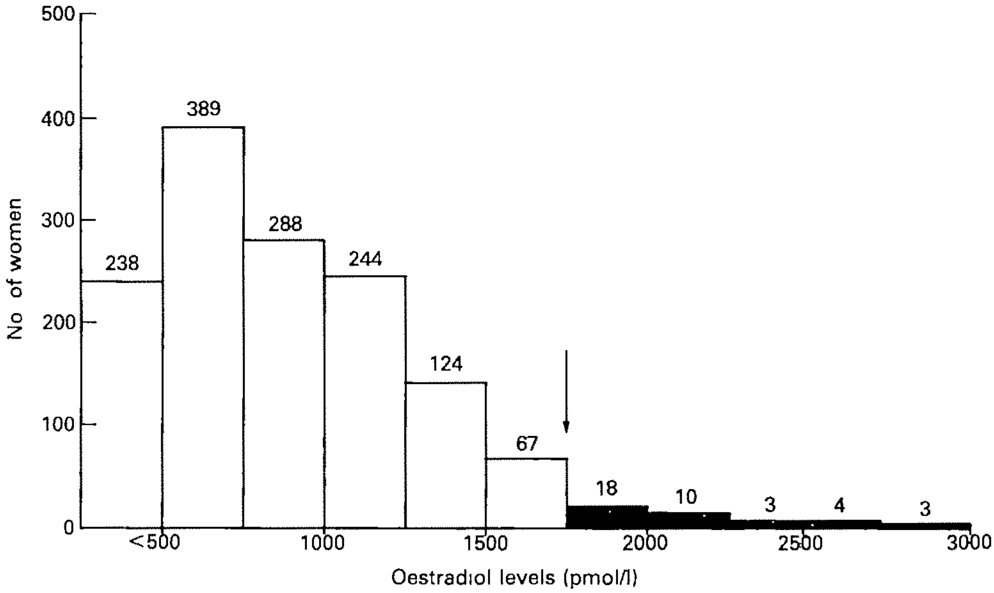

Fig. 1. Distribution of serum oestradiol levels at time of re-implantation in 1388 women treated with oestradiol implants for the premenstrual syndrome or menopausal symptoms

severe oestrogen-dependent depression return sooner to the clinics in order to maintain the serum oestradiol levels at a supraphysiological level necessary for relief of these symptoms. However, all of these 38 women considered that they were in better health at the time of alleged return of symptoms than at their first visit. Hence, their reattendance may also indicate increased and even unreasonable expectations of an extra improvement in their general well-being.

There is some anxiety about the possible harmful sequelae of supraphysiological oestradiol levels but no data are currently available to show any deleterious effects of these levels on coagulation factors, blood pressure, glucose tolerance or the occurrences of endometrial or breast cancer (Hammond *et al.* 1974; Thom *et al.* 1978; Studd & Thom 1981; Armstrong 1988). Increased levels of oestradiol may be beneficial, not only for their anti-depressant effect, but also in their effect upon bone density. The latter is greater after implant therapy than after oral therapy and is related to the greater plasma oestradiol levels achieved in women with implants (Savvas *et al.* 1988).

None of the 38 patients complained of alleged symptoms of oestrogen excess, such as breast tenderness, fluid retention or nausea.

Oestrogen replacement therapy is a major development in preventative medicine The aim in most women is to return the plasma oestradiol to normal physiological values as this is usually adequate for relief of symptoms and protection of the skeletal and cardiovascular systems. Implants of 50 mg of oestradiol given at 6-month intervals are ideal for this purpose and will not lead to supraphysiological oestradiol levels It is the increasing frequency of implantation which causes plasma oestradiol levels to rise but for selected women with severe depression or PMS these levels of oestradiol may be a therapeutic requirement. This is not true tachyphylaxis as these women require high oestradiol levels in order to remain symptom-free. In this respect implants are to be preferred as oral treatment fails to achieve such high oestradiol levels and the continuous use of 100 μg patches is fre-

Table 1. Clinical details of 38 women with supraphysiological oestradiol (E2) levels after hormone implant therapy for the premenstrual syndrome (PMS) or menopausal symptoms *

Subjects	Age at start of treatment (years)	Duration of treatment (years)	Mean interval between implants (months)	Most recent dosage	Serum E2 level (pmol/l)
PMS					
1	47	6	4	E75	1920
2	44	12	4	E75 T100	2815
3	54	12	4	E100 T100	2030
4	36	2	4	E100 T100	2005
5	45	4	4	E50 T100	1930
6	41	2	4	E75 T100	2820
7	36	2	6	E75	2265
8	37	4	5	E75	2175
9	39	5	4	E75	2220
10	39	11	6	E100 T100	1930
11	43	10	6	E75 T100	2060
12	45	7	6	E100 T100	1760
13	38	3	4	E50 T100	2575
14	34	1	4	E75 T100	2025
15	37	2	4	E75 T100	1760
Menopausal					
16	49	6	4	E100 T100	2555
17	54	1	3	E100 T100	2020
18	52	5	4	E100 T100	2020
19	42	3	3	E100	2040
20	42	4	3	E100	1915
21	48	7	4	E50	1875
22	58	4	4	E50 T100	1785
23	48	2	3	E75	1815
24	46	3	4	E75	1815
25	51	4	4	E75	2015
26	52	3	4	E50	1920
27	29	9	4	E50 T100	2540
28	33	9	4	E50 T100	1830
29	38	10	6	E50 T100	1975
30	47	5	5	E50 T100	1940
31	36	3	4	E75 T100	2925
32	50	4	4	E75	2000
33	48	6	6	E75	1815
34	48	2	3	E75	1765
35	42	3	4	E75 T100	2270
36	53	2	4	E75 T100	1790
37	40	3	5	E50 T100	2380
38	55	7	6	E50	1860

*Twenty women (subjects 1–9 and 16–26) had a psychiatric history, and nine women (subjects 27–35) had a surgical menopause.

quently associated with adverse skin reactions (Savvas *et al.* 1988). Complete withdrawal of oestrogen therapy as suggested by Gangar *et al.* (1989), to allow levels to return to 200 pmol/l is wrong and in severely depressed patients may be dangerous.

Supraphysiological oestradiol levels are an uncommon consequence of oestradiol implants occurring most frequently in women with a history of depression or surgical castration. These high serum oestradiol levels were not associated with any deleterious effects and may be necessary for the control of symptoms in specific women.

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A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer

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Summary. Age, ultrasound score, menopausal status, a clinical impression score and serum CA 125 level were assessed to see how they could best distinguish between patients with benign ($n = 101$) and malignant ($n = 42$) pelvic masses. Each criteria used alone provided statistically significant discrimination. The most useful individual criteria were a serum CA 125 level of 30 U/ml (sensitivity 81%, specificity 75%) and an ultrasound score of 2 (sensitivity 71%, specificity 83%). Three criteria could be combined in a risk of malignancy index (RMI) which is simply calculated using the product of the serum CA 125 level (U/ml), the ultrasound scan result (expressed as a score of 0, 1 or 3) and the menopausal status (1 if premenopausal and 3 if postmenopausal). This index was statistically virtually as effective a discriminant between cancer and benign lesions as more formal methods. Using an RMI cut-off level of 200, the sensitivity was 85% and the specificity was 97%. Patients with an RMI score of greater than 200 had, on average, 42 times the background risk of cancer and those with a lower value 0·15 times the background risk.

The greatest opportunity to influence the natural history of ovarian cancer occurs at the time of the initial laparotomy. The aims of surgical management at this time are to determine accurately the extent of disease and to reduce residual tumour volume to a minimum (Griffiths 1987 Hacker 1987). In spite of the knowledge of the benefits of accurate surgical staging and cytoreductive surgery, many patients do not receive appropriate surgery at the time of surgical diagnosis (Young *et al.* 1983). Adequate treatment at primary laparotomy is generally considered to require persistent, time consuming and aggressive surgery that is often not feasible during a routine operating list. Ideally, patients with ovarian malignancy should therefore be referred

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for primary laparotomy to a surgeon with appropriate operative experience and resources. In practice, the diagnosis of ovarian cancer is often difficult to make preoperatively and inadequate surgical exploration by junior or inexperienced surgeons is a regular occurrence. Sensitive and specific methods for preoperative diagnosis of ovarian cancer would provide a rational basis for referral before diagnostic laparotomy. Patients with ovarian cancer could thereby be ensured of the benefits of thorough surgical staging and cytoreduction by an experienced surgeon.

This department is currently conducting a systematic assessment of biochemical and biophysical diagnostic tests for the detection of ovarian cancer (Jacobs *et al.* 1988, 1989) We describe here our assessment of the value of clinical features, real time ultrasonography and serum CA 125 measurement in the diagnosis of 143 consecutive patients admitted with an adnexal mass.

Patients and methods

The study included 143 patients admitted consecutively to the Gynaecology Department at The London Hospital for elective surgical investigation of an adnexal mass. All of them gave informed consent.

Clinical data

A standardized computer data sheet has been used to record socio-demographic characteristics, past medical history, the history of the current condition, and findings on physical examination.

Clinical impression

One individual (I. J.) assessed each patient on the basis of all the information obtained preoperatively by the clinical team. This assessment was made with access to the clinical history, the physical examination and the results of any investigations done before operation such as haematology, biochemistry, chest X-ray, ultrasound, intravenous urogram, but without knowledge of the serum CA 125 level. Clinical impression was scored on a scale of 1–5, (1 = benign, 2 = probably benign, 3 = uncertain, 4 = probably malignant, 5 = malignant).

Ultrasound scan

An ultrasound scan was performed as part of routine preoperative assessment on all but four patients (one with malignant disease, three with benign disease) by the staff of the Radiology department at The London Hospital. All the scans were performed via the abdominal route with the full bladder technique, using a Diasonics DS.1 sector scanner with a 3·5 MHz transducer. Ultrasound reports were scored 1 point for each of the following characteristics; (i) multilocular cyst, (ii) evidence of solid areas, (iii) evidence of metastases, (iv) presence of ascites and (v) bilateral lesions.

Radioimmunoassay

Peripheral venous blood samples were obtained preoperatively from each patient. Blood samples were allowed to clot at room temperature and then centrifuged at 3000 rpm for 10 min. The serum was separated, aliquoted and stored at minus 20°C. Serum CA 125 level was determined by radioimmunoassay (Abbott Laboratories CA 125 RIA, Chicago, USA). The intraassay and interassay coefficients of variation were <10%.

Table 1. Histological type and FIGO stage of 42 patients with malignant disease

Histological type	FIGO stage				Total
	I	II	III	IV	
Serous cystadenocarcinoma	1	0	10	1	12
Mucinous cystadenocarcinoma	2	0	4	0	6
Endometrioid adenocarcinoma	1	1	2	0	4
Clear cell carcinoma	1	1	2	0	4
Undifferentiated carcinoma	1	1	8	0	10
Borderline malignancy	4	0	0	0	4
Dysgerminoma	1	0	0	0	1
Metastatic bowel adenocarcinoma	—	—	—	—	1

Table 2. Statistically significant differences between 101 patients with benign and 42 with malignant pelvic masses

Variable	Benign ($n = 101$)	Malignant ($n = 42$)	Significance level	
			P	Test
Age (years)				
mean (SD)	48·8(14·3)	59·0(11·8)	<0·001	t test
Postmenopausal (%)	48·0	80·5	<0·001	χ^2
Clinical impression score				
median (range)	2(1–4)	4(3–5)	<0·0001	U test
Ultrasound score				
median (range)	1(0–2)*	2(1–2)†	<0·0001	U test
Serum CA 125 (U/ml)				
mean (95% CI)	17·5(4·3–70·2)	122·0(6·1–3394·8)	<0·0001	t test

*n=98, †n=41.

Histological or surgical diagnosis

When a surgical specimen was sent for pathological examination a copy of the report was obtained. When a specimen was not sent for histological examination, the surgical diagnosis was assumed to be correct (e.g., follicular cysts).

Statistical analysis

Postmenopausal status is defined as >1 year of amenorrhoea or age over 50 years for women who had previously undergone a hysterectomy ($n = 11$). Comparison between patients with benign and malignant disease was performed using the Student's t-test for age, the χ^2-test for menopausal status and the Mann Whitney U test for ultrasound score and clinical impression. As CA 125 is approximately log normally distributed (Jacobs *et al.* 1988). Student's t-test was used to compare log transformed values of serum CA 125 in patients with benign and malignant disease.

Sensitivity was defined as the percentage of

Table 3. Sensitivity and specificity of age, menopausal status, clinical impression, ultrasound and serum CA 125 level in the differential diagnosis of benign and malignant masses in 143 patients

Test and action line	Sensitivity (%)	Sensitivity (95% CI)	Specificity (%)	Specificity (95% CI)
Age (years)				
40	90·5	(77·4- 97·3)	27·7	(19·5- 37·9)
50	78·6	(63·2- 89·7)	53·5	(43·7- 64·0)
60	54·3	(38·7- 70·2)	75·2	(65·3- 83·1)
70	16·7	(7·0- 31·4)	96·0	(90·1- 98·9)
Post-menopausal	78·6	(63·2- 89·7)	52·5	(42·3- 62·6)
Clinical impression score				
3	100·0	(91·6-100·0)	54·5	(44·2- 64·5)
4	64·3	(48·0- 78·5)	71·3	(61·4- 79·9)
5	9·5	(2·7- 22·6)	100·0	(96·4-100·0)
Ultrasound score*				
1	100·0	(91·4-100·0)	46·9	(36·8- 57·3)
2	70·7	(54·5- 83·9)	82·7	(73·7- 89·6)
Serum CA 125 (U/ml)				
30	81·0	(65·9- 91·4)	75·2	(65·5- 83·3)
50	66·7	(50·5- 80·4)	94·1	(87·5- 97·9)
70	61·9	(45·6- 76·4)	98·0	(93·0- 99·8)
90	57·1	(41·0- 72·3)	99·0	(94·6-100·0)

*The ultrasound data includes only 139 patients.

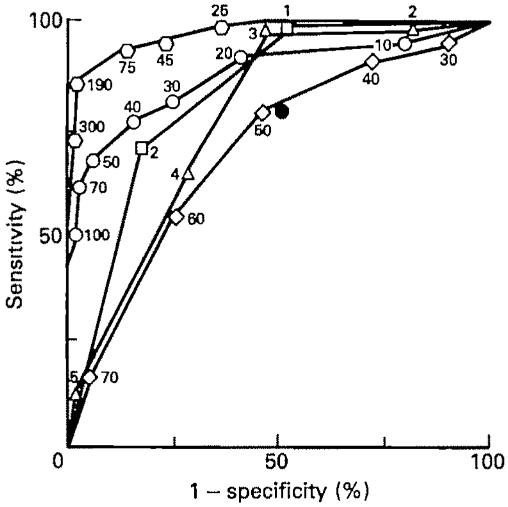

Fig. 1. Receiver operator characteristics of various criteria in the preoperative prediction of the benign or malignant nature of an adnexal mass The upper limits for different combinations of specificity and sensitivity for age (years), clinical impression score (1–5), ultrasound score (0–2), serum CA 125 level (U/ml) and risk of malignancy index score (25–300) are shown next to the symbols. Menopausal status is represented by a single point. △ Clinical impression score; ● Postmenopausal status; ◇ Age (years), ◯ RMI (risk of malignancy index); □ Ultrasound score; ○ CA 125 (U/ml)

patients with malignant disease who had a positive test result and specificity as the percentage with benign disease who had a negative test result. Exact confidence intervals for sensitivity and specificity were calculated from the binomial distribution. The likelihood ratio (LR) of malignancy associated with a test result is defined as the odds for malignancy in patients with the test result, divided by the odds for malignancy in the entire population (the prior odds). The LR is therefore independent of the prevalence of malignant disease in the particular population studied, and can be generalised to predict risks of malignancy in other populations, by multiplying the LR by the prior odds for malignancy in that population. Stepwise logistic regression was performed using the BMDP statistical package (program PLR). The four patients who did not have a preoperative ultrasound scan were excluded from the logistic regression analysis. In performing the logistic regression analysis, clinical impression score was omitted because of its subjective nature. Logistic regression analysis provided a formula for calculation of the likelihood ratio associated with a patient's menopausal status, ultrasound score and serum CA 125 level. This formula was simplified without loss of diagnostic precision to provide a risk of malignancy index (RMI) suitable for use in clinical practice.

Results

Benign gynaecological conditions including benign ovarian tumours (70), functional ovarian cysts (11), endometriosis (6), fibroids (6), pelvic adhesions (4) and fimbrial cysts (2) were diagnosed in 99 patients; no abnormality was detected in two patients. The histological diagnosis and FIGO stage in the 42 patients found to have malignant disease is summarized in Table 1. Primary invasive epithelial ovarian malignancies were found in 36 women and were most commonly stage III and of serous or undifferentiated histological type.

Individual criteria

Statistically significant differences between the benign and malignant groups were observed for age, menopausal status, clinical impression score, ultrasound score and serum CA 125 level (Table 2). There was no significant association apparent between other features of the history, presentation or physical examination and the presence of benign or malignant disease. A sensitivity and specificity greater than 70% were achieved only by serum CA 125 (upper limit between 30 U/ml and 40 U/ml) and ultrasound (score of 2) (Table 3). A further three criteria achieved a sensitivity and specificity greater than 70% and 50% respectively (age 50 years, postmenopausal status and a clinical impression score of 3).

Combinations of criteria

Stepwise logistic regression analysis revealed that menopausal status, ultrasound score and serum CA 125 level were all significantly ($P <$ 0·01) and independently related to the likelihood ratio for malignancy. Age was not significantly related to the likelihood ratio nor were any interaction terms significant. The risk of malignancy index (RMI) was derived from the logistic regression analysis (as described in the appendix) and was defined as follows:

$$\text{RMI} = U \times M \times \text{serum CA 125}$$

where;
$U = 0$ for ultrasound score of 0
$= 1$ for ultrasound score of 1
$= 3$ for ultrasound score of 2–5

$M = 1$ if premenopausal
$= 3$ if postmenopausal

Examples: (1) A premenopausal patient with a serum CA 125 level of 40 U/ml and two ultrasound features of malignancy would have an RMI score of 120 ($U = 3$, $M = 1$, CA $125 = 40$). (2) A postmenopausal patient with the same ultrasound and CA 125 results would have an RMI of score 360 ($U = 3$, $M = 3$, CA $125 = 40$). (3) All patients with no ultrasound features of malignancy would have an RMI score of zero regardless of their menopausal status or serum CA 125 result ($U = 0$).

The performance of the RMI at various upper limits is illustrated in Fig. 1 and can be seen to combine higher levels of specificity and sensitivity than were achieved by individual criteria. The relation between menopausal status, ultrasound score and serum CA 125 level is illustrated in Fig. 2.

Superimposed on Fig. 2 are action lines defined by RMI levels which achieved useful combinations of specificity and sensitivity. Table 4 shows the sensitivity, specificity and the likelihood ratio for malignancy given a positive result for different levels of the RMI. An RMI of 200 achieved a sensitivity of 85·4% (95% CI, 70·8%–94·4%) and a specificity of 96·9% (95% CI, 91·3%–99·4%). The likelihood ratio for malignancy of patients predicted to have benign and malignant disease by an RMI of 200 was 0·15 and 42·1 respectively, representing a 280 fold difference in the odds for malignancy.

Discussion

The RMI provides a novel method for assessing the risk of malignant disease in patients with an adnexal mass. The combination of three criteria (ultrasound, menopausal status and serum CA 125 level) in the RMI provided a level of discrimination between benign and malignant disease greater than could be achieved by individual criteria alone. Furthermore, the RMI was more reliable as a diagnostic discriminator than a clinical assessment of all diagnostic criteria available preoperatively (the clinical impression score). Diagnostic accuracy could not be improved by consideration of age or clinical criteria in addition to the three criteria included in the RMI.

The RMI provides a quantitative assessment of the risk of malignancy and can be used to discriminate between benign and malignant disease in the same way as other variables Various upper limits for the RMI combined higher levels of sensitivity and specificity than individual criteria (Fig. 1) The action line selected for clinical decision making will depend upon the balance between sensitivity and specificity appropriate to local resources. A low action line such as a RMI of 50 may be preferable when limitations on referral for specialist care are minimal. Where the availability of specialist care is limited because of distance or resources, some degree of sacrifice in sensitivity to achieve high levels of specificity may be appropriate. The action line can then be set at a higher RMI level for instance at 75 or 200. A clinician selecting patients for specialist management in this way would expect to classify correctly approximately 90% of patients with a benign or malignant adnexal mass preoperatively.

Table 4. The sensitivity, specificity and the likelihood ratio for malignancy given a positive or negative result for different levels of the risk of malignancy index (RMI)

RMI score	Sensitivity		Specificity		Likelihood ratio for malignancy if result is	
	(%)	(95% CI)	(%)	(95% CI)	Positive	Negative
25	100·0	(91·4–100·0)	62·2	(51·9-71·8)	2·7	0·00
50	95·1	(83·5–99·4)	76·5	(66·9–84·5)	4·1	0·06
75	92·7	(80·1–98·5)	84·7	(76·0–91·2)	6·1	0·09
100	85·4	(70·8–94·4)	87·8	(79·6–93·5	7·0	0·17
150	85·4	(70·8–94·4)	93·9	(87·2–97·7)	14·0	0·16
200	85·4	(70·8–94·4)	96·9	(91·3–99·4)	42·1	0·15
250	78·0	(62·4–89·4)	99·0	(94·5–100·0)	76·9	0·22

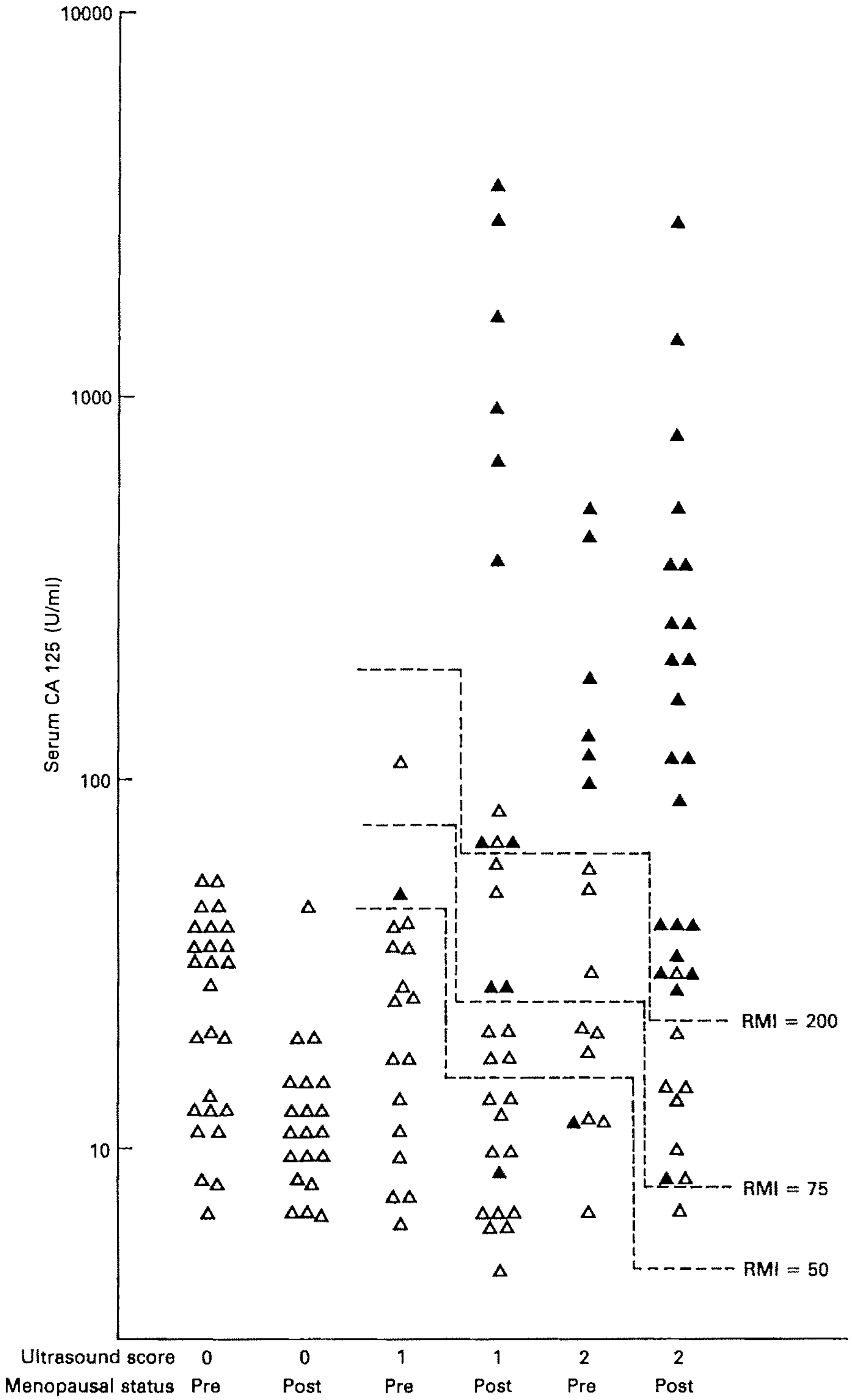

Fig. 2. The relation between menopausal status, ultrasound score, serum CA 125 level and clinical impression score in 139 patients with benign (open symbols) and malignant (closed solid symbols) adnexal masses. Broken lines represent action lines for risk of malignancy index (RMI) scores of 50, 75 and 200. (Note that all individuals with an ultrasound score of 0 will have an RMI score of zero)

The likelihood ratio and logistic regression analysis are independent of the ratio of benign to malignant disorders in the study population. The RMI, which was derived from the logistic regression formula, can therefore be generalized to populations with a prevalence of benign and malignant disease other than that observed in the London Hospital population. The performance of the RMI in discriminating patients with benign and malignant disease was slightly inferior to the best possible discrimination based on menopausal status, ultrasound score and serum CA 125. However, because of its association with the likelihood ratio, the RMI is more likely to be robust and applicable to other populations than a rule based on the best possible discrimination.

The ultrasound findings in this study confirm previous reports that features such as multiloculation, solid areas, ascites and bilaterality that are more frequently associated with malignant masses, may also be identified with benign disease (Herrmann *et al.* 1987, Moyle *et al.* 1983, Koyabashi 1976, Meire *et al.* 1978, Deland *et al* 1979) (Fig. 2). Although an ultrasound score of 2 was associated with a high risk of malignancy, the clinical value of ultrasound as an individual test was limited by the observation of features of malignancy in 52 patients with benign disease. The main value of ultrasound was the reliable exclusion of malignant disease. The absence of ultrasound evidence of solid areas, multiloculation, bilaterality, ascites or metastatic disease was uniformly associated with the presence of benign disease.

The diagnostic sensitivity and specificity of serum CA 125 measurement in this study was comparable to previous reports (Einhorn *et al.* 1986, Vasilev *et al.* 1988, Malkasian *et al.* 1988, Patsner *et al.* 1988, Di-Xia *et al.* 1988). The limitation of serum CA 125 measurement was the occurrence of moderately elevated serum CA 125 levels in benign disease. In contrast to ultrasound the main value of serum CA 125 estimation was the reliable prediction of the presence of malignant disease in the group of patients with high serum CA 125 levels (Fig. 2). Although patients with a serum CA 125 level greater than 70 U/ml were at particularly high risk of malignancy the sensitivity of an action line of 70 U/ml or more was relatively low (Table 3).

Previous studies have noted that discrimination between benign and malignant disease may be improved by combined consideration of CA 125 and menopausal status (Malkasian *et al.* 1988), CA 125 and other tumour markers (Yedema *et al.* 1988, Knauf and Bast 1988) or CA 125 and ultrasound (Gadducci *et al.* 1988). However, a systematic basis for combined consideration of these criteria has not been defined. To our knowledge the RMI is the first report of a simple diagnostic index, suitable for use in clinical practice, which defines the optimal combination of diagnostic criteria. The ability of the RMI to distinguish between benign and malignant disease reflects the complementarity of ultrasound findings and serum CA 125 levels. Few patients with malignant disease and an elevated serum CA 125 level had low ultrasound scores, whilst most patients with benign disease and an elevated serum CA 125 level had ultrasound scores of 0 or 1 (Fig. 2). It was therefore possible to improve specificity with minimal sacrifice of sensitivity. Further refinement of the RMI to achieve greater diagnostic accuracy may be possible using additional tumour markers and by the application of Doppler blood flow imaging to ovarian tumours (Bourne *et al.* 1989).

The available evidence suggests that the outlook for ovarian cancer is influenced by the quality of the primary surgical procedure. Application of the RMI in clinical practice would provide a rational basis for specialist referral of patients with malignant disease before diagnostic surgery. A larger proportion of ovarian cancer patients would as a result undergo optimal staging and cytoreduction. Whether the introduction of the RMI into clinical practice will actually be translated into an improvement in prognosis for ovarian cancer patients is the subject of ongoing research.

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Appendix: Derivation of the risk of malignancy index (RMI)

The model for the log odds ratio (OR) provided by stepwise logistic regression analysis was·

$$\text{Log (OR)} = a + [b \times \log (\text{CA } 125)] + [c \times \text{US}] + [d \times \text{MS}] \qquad (1)$$

where;
US = ultrasound score
$a = -10{\cdot}46$
$c = 1.77$ (SE $= 0{\cdot}69$)
MS = menopausal score
$b = 1{\cdot}71$ (SE $= 0{\cdot}41$)
$d = 1{\cdot}86$ (SE $= 0{\cdot}76$)

Attempts were made to improve the fit of this model by incorporating squared terms (to test for curvature) and various interaction terms (to test for independence of risk factors) but no variable was associated with risk not explained by CA 125, ultrasound score and menopausal status at the 1% level. Equation (1) was converted to a formula for the odds ratio by raising to the power e and rearranging:

$$\text{OR} = 1{\cdot}68 \times 10^{-4} \times (U \times M \times \text{CA } 125)^{1\ 71} \qquad (2)$$

where,
$U = 0$ if ultrasound score is 0
$U = 1$ if ultrasound score is 1
$U = 2.82$ if ultrasound score is 2
$M = 1$ if premenopausal
$M = 2\ 97$ if postmenopausal

Formula 2 was converted to a formula for the likelihood ratio (LR) in the population by dividing by the prior odds ratio in the population (42/101). A rearrangement gave the following.

$$\text{LR} = (U \times M \times \text{CA } 125/96\ 3)^{1\ 71} \qquad (3)$$

This exact formula for the likelihood ratio was simplified to provide the risk of malignancy index (RMI). The performance of the RMI in differentiating between benign and malignant disease was identical to the true LR given by formula (3), (i e , at any chosen specificity their sensitivities were equal).

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Serum CA 125 levels during the menstrual cycle

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Summary. Serum concentrations of CA 125 were measured in different phases of the menstrual cycle in 16 women with ovulatory and 12 women with anovulatory cycles. CA 125 levels were significantly elevated during menstruation in both groups. In women with anovulatory cycles, but not in those with ovulatory cycles, CA 125 levels were already increased in the premenstrual phase. A negative correlation was found between serum CA 125 and progesterone concentrations in the premenstrual phase of the cycle. We suggest that premenstrual elevation of serum CA 125 in women with anovulatory cycles is related to premature endometrial vascular changes which are the result of the low serum progesterone concentration leading to insufficient endometrial control. Thus the effect of progesterone seems to be indirect rather than a direct effect on CA 125 synthesis. When the CA 125 assay is used for diagnosis of cancer, sampling should not be done immediately before or during menstruation because the physiological elevation of the CA 125 levels may give false positive results.

Serum CA 125 concentration is increased in over 80% of patients with ovarian cancer (Bast *et al.* 1983; Halila *et al.* 1988). The specificity of the CA 125 test has given promise for this assay as a potential component of a strategy aimed at the early detection of ovarian cancer (Zurawski *et al.* 1987; Jacobs *et al.* 1988a). However, previous reports have shown that some benign diseases like endometriosis (Barbieri *et al.* 1986; Giudice *et al.* 1986; Patton *et al.* 1986; Masahashi *et al.* 1988) and even normal physiological events like pregnancy (Halila *et al* 1986) and menstrual bleeding (Mastropaolo *et al.* 1986; Pittaway & Fayez 1987; Masahashi *et al.* 1988) may elevate serum CA 125 levels. Therefore, to avoid misinterpretation of elevated CA 125 levels during menstruation, the exact timing of blood sampling is important.

The physiological changes in serum CA 125 concentrations may indicate that it is under hormonal control. A progesterone-induced elevation of serum CA 125 levels has been reported in patients with endometriosis (Ozasa *et al.* 1987). On the other hand, CA 125 production was not affected by oestrogen, progestin or tamoxifen in immunodeficient mice inoculated with ovarian carcinoma (Holt *et al.* 1987).

The aim of our study was to measure serum CA 125 levels in different phases of the menstrual cycle and to examine a possible association with ovarian sex steroids.

Subjects and methods

Twenty-eight apparently healthy young women (mean age 20, range 15–32 years) were selected for the study; 20 were <18 years of age. Of the 28 women, 16 had normal menstrual cycles with luteal phases of at least 10 days and a serum pro-

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gesterone concentration >10 nmol/l. The length of the luteal phase was estimated on the basis of LH and progesterone concentrations. In 12 women aged 15–18 years, serum progesterone concentration remained below 10 nmol/l throughout the cycle, and these cycles were classified as anovulatory. The cycles were divided into four phases: (1) cycle days 1–7; (2) cycle days 8–18; (3) last 7 days of cycle; (4) cycle days 1–7 of the next cycle. Thus phase 4 corresponds to phase 1. Blood samples were collected every 3–4 days during phases 1, 3 and 4 and every 1–2 days during the estimated periovulatory period in phase 2. The specimens were grouped retrospectively into appropriate phases. Serum samples were stored at −20°C until assayed for CA 125, progesterone, oestradiol and LH.

An immunoradiometric CA 125 assay was used according to the manufacturer's instructions (Abbott Laboratoriers, Wiesbaden, FRG). The sensitivity of the assay was 6.4 U/ml. Levels >35 U/ml were considered elevated (Bast *et al.* 1983). To compare CA 125 levels during the menstrual cycle, the values were expressed as a percentage of the mean value of all observations for each individual. Serum progesterone, oestradiol and LH concentrations were measured by routine radioimmunoassays.

The data were analyzed by BMDP programs (BMDP Statistical Software of 1987, University of California, Los Angles, CA). Statistical assessment used analysis of variance for repeated measurements and the paired Student's *t*-test within the phases of the cycle and Mann-Whitney *U*-test between the ovulatory and anovulatory cycles.

Results

CA 125 levels were significantly higher during the first week (phases 1 and 4) of the cycle than during the middle part (phase 2) of the cycle both in women with ovulatory and in those with anovulatory cycles (Table 1). The highest concentrations of CA 125 in ovulatory and anovulatory women during menstruation were 51 U/ml and 125 U/ml, respectively. In women with anovulatory cycles, but not in those with ovulatory cycles, CA 125 levels were already significantly increased before the outset of menstruation (phase 3). CA 125 levels were slightly higher in the anovulatory than in the ovulatory group, but the difference was statistically significant only in phase 3 (Table 1 and Fig. 1). There was a negative correlation ($r = -0{\cdot}48$, $P<0{\cdot}001$) between serum progesterone concentration and CA 125 expressed as a percentage of the individual mean value (Fig. 2). As progesterone decreased in ovulatory cycles, CA 125 levels increased, whereas in anovulatory cycles, most CA 125 values were increased above the mean level throughout the last week of the cycle. In ovulatory cycles there were no differences in CA 125 levels between women below and above 18 years of age.

Table 1. Serum CA 125 (U/ml) concentrations during different phases of ovulatory and anovulatory menstrual cycles

	Cycle phase			
	1	2	3	4
Ovulatory cycles				
Mean (SE)	16·0 (2·2)	10·9 (1·4)	11·5 (1·1)	16·8 (3·9)
Max	37	24	27	51
Number of subjects	15	16	16	8
P^a	0·0005	Ns	Ns	
P^b	Ns	Ns	0·04	Ns
Anovulatory cycles				
Mean (SE)	17·6 (4·0)	12·3 (1·4)	16·7 (2·4)	25 (9·3)
Max	43	26	36	125
Number of subjects	10	12	12	12
P^a	0·004	0·001	Ns	

P^a denotes the significance of the difference between the sequences of the cycles.

P^b denotes the significance of the difference between the groups of ovulatory and anovulatory cycles

Mean values for each individual within each phase were calculated from 1–3 samples and the individual mean was used to calculate the mean values for the groups. However, maximum values (Max) represent the highest individual maximum values within each phase. The minimum value is equal to the detection limit 6·4 U/ml

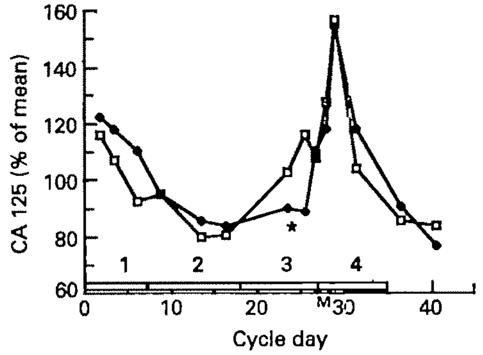

Fig. 1. Serum concentrations of CA 125 during ovulatory (—◆—) and anovulatory (—□—) menstrual cycles expressed as a percentage of mean value of all measurements of each individual ($n = 28$) Phases 1–4 denote cycle days 1–7, cycle days 8–18, 1–7 days before the onset of the next menstruation, and cycle days 1–7 of the next cycle, respectively M = Onset of menstruation. *Indicates a significant difference ($P = 0{\cdot}04$) between ovulatory and anovulatory cycles in phase 3.

No significant correlations were found between CA 125 and serum oestradiol in any groups or sequences. The midcycle rise of serum oestradiol in the ovulatory group had no influence on CA 125 concentration (Fig. 1). There was no significant difference in maximal serum oestradiol concentrations between the women with ovulatory (mean 0·38, SE 0·12) and anovulatory cycles (mean 0·78, SE 0·11 nmol/l)

Discussion

Serum CA 125 levels were significantly elevated during menstruation, which is consistent with previous reports (Mastropaolo *et al* 1986; Pittaway & Fayez 1987; Masahashi *et al.* 1988). New findings were the rise in CA 125 concentrations during the premenstrual phase and the higher levels in women with anovulatory cycles compared with those with ovulatory cycles. Because anovulatory cycles occurred in the age group 15–17.5 years, we compared the CA 125 levels in ordinary cycles of women above and below 18 years of age and found no difference. This indicates that the differences in CA 125 level were related to anovulation and not to age. The frequency of anovulatory cycles in the present study was fairly high, because two-thirds of the subjects were adolescents, in whom anovulation is common (Apter *et al.* 1980).

In nonpregnant women endometrium appears to synthesize CA 125 (Jacobs *et al.* 1988b) and women with normal serum CA 125 concentrations have high levels in cervical mucus. This indicates that there is a barrier to CA 125 between the normal uterine epithelium and blood circulation (de Bruijn *et al.* 1986; Jacobs *et al.* 1988b). We suggest that the breakdown of this barrier allows CA 125 to diffuse into peripheral blood causing increased concentrations of CA 125 during menstruation. As about 25% of the serum samples obtained in the middle part of the cycles had CA 125 levels below the detection limit of 6.4 U/ml, the real differences between various phases of the cycle are probably greater than those observed.

It has been suggested that CA 125 in cervical mucus is under the control of ovarian sex steroids because significantly higher levels have been found in the follicular than in the luteal phase of the normal menstrual cycle (de Bruijn *et al.* 1986; Fujii *et al.* 1988). Exogenous ethinyl oestradiol also caused an increase in cervical mucus CA 125 but not in serum levels (de Bruijn *et al.* 1986). On the other hand, no significant difference was found between CA 125 levels in proliferative and secretory endometrium (Jacobs *et al.* 1988b). Our results agree well with this because we did not find any influence of serum oestradiol or progesterone on serum CA 125 in the normal cycles before the end of the cycle. We found a negative correlation between serum CA 125 and progesterone levels during the last week of the cycle. In a previous study, serum CA 125 was reported to increase after injection of progesterone in patients with endo-

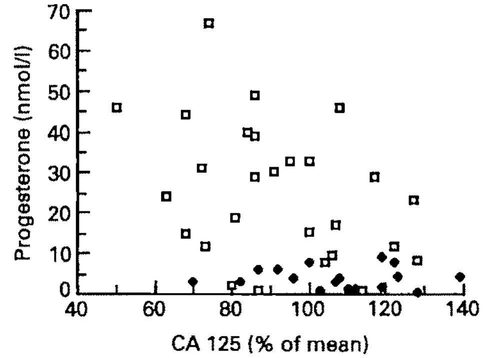

Fig. 2. Serum CA 125 expressed as a percentage of mean value of all measurements of each individual and progesterone concentrations of 46 samples from 16 ovulatory (□) and 12 anovulatory (◆) cycles during the last week of the cycle (phase 3) The coefficient of correlation was $-0{\cdot}48$, $P<0{\cdot}001$.

metriosis but not in women without endometriosis (Ozasa *et al.* 1987), but, serum progesterone concentrations were not measured in that study, so that a relation could not be established.

The normal endometrium is structurally stable and under strict control of the ovarian sex steriods. Withdrawal of oestrogen and progesterone at the end of the cycle initiates vasomotor events in the endometrium leading to vasoconstriction, ischaemia and stasis about 24 h before the onset of menstruation. In cycles with insufficient serum progesterone levels the endometrium is unstable and disarrangement of the endometrium appears earlier (Speroff *et al.* 1983). This may allow CA 125 to escape into the blood circulation causing elevated serum leaves some days before the onset of menstruation as we found in this study. We suggest that the premenstrual elevation of serum CA 125 level in women with anovulatory cycles is related to premature endometrial vascular changes which are the result of the low serum progesterone concentrations leading to insufficient endometrial control. Thus the effect would not be a direct effect of progesterone on CA 125 synthesis.

When CA 125 determinations are used for diagnosis of cancer, sampling should not be done immediately before or during menstruation because of the cyclic variations of serum CA 125 levels. To avoid this problem, the best time for sampling is the period beginning after menses and ending one week before the onset of the next menstruation.

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The effect of abdominal surgery on the serum concentration of the tumour-associated antigen CA 125

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Summary. The CA 125 assay is used to monitor the course of disease in women with adenocarcinoma of the genital tract. We measured serum CA 125 levels longitudinally in three different groups of patients who had normal serum CA 125 levels (≤16 U/ml) before extensive intraperitoneal abdominal surgery (group 1, second-look laparotomy in 28 women with ovarian cancer; group 2, radical hysterectomy in 42 patients with cervical cancer; group 3, 13 men and one woman who had aortic surgery for atherosclerotic occlusive disease or aneurysm formation). Following surgery, rising serum CA 125 levels were observed in 69 out of the 84 patients (82%), irrespective of the primary diagnosis, type of operation or sex. The highest levels were found during the second week after the operation (range 3–336 U/ml) and decreased gradually thereafter, to become normal at 8 weeks after surgery. It was concluded that abdominal surgery interferes with the specificity of CA 125 as a tumour marker during the early postoperative period.

The tumour-associated antigen CA 125 has been shown to be an adequate tumour marker in women with adenocarcinoma of the genital tract (Bast *et al.* 1983; Duk *et al* 1986; Schilthuis *et al.* 1987; Duk *et al.* 1989*a*; Jacobs & Bast 1989). Serial serum CA 125 determinations are used to assess the effects of therapy. Increasing serum CA 125 concentrations predict renewed tumour activity or disease progression. There is supportive histopathological evidence that the increase in serum CA 125 concentrations may be due to the infiltrative growth of tumour cells in association with alteration in tissue barriers (Fleuren *et al.* 1987). Serum CA 125 concentrations also increase as a result of reactive changes in mesothelial cells due to a variety of non-malignant stimuli (Mezger *et al.* 1987). In patients treated for gynaecological malignancies, we have frequently observed a transient rise in the serum CA 125 level following extensive surgery, such as radical hysterectomy or second-look laparotomy, that was not clinically related to tumour proliferation. Such a postoperative rise in the serum CA 125 level interferes with the clinical usefulness of the assay. Redman *et al.* (1988) found high CA 125 concentrations in the peritoneal lavage fluid obtained during abdominal surgery, whereas the serum CA 125 levels were normal. In contrast, Talbot *et al.* (1989) reported

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increasing serum CA 125 levels following abdominal surgery. These contradictory observations prompted us to conduct a quantitative investigation of the effect of abdominal surgery on the serum CA 125 levels in three different groups of patients having abdominal surgery.

Subjects and methods

The study population consisted of three groups of patients who had intraperitoneal abdominal surgery between July 1987 and December 1988 at the Department of Obstetrics and Gynaecology and the Department of Surgery of the University Hospital of Groningen, the Netherlands. All patients were selected on the basis of a normal pre-operative serum CA 125 level.

Group 1 consisted of 28 patients who were treated for Stage III epithelial ovarian cancer. Tumour stage had been established at primary debulking laparotomy according to the classification criteria of the International Federation of Gynaecology and Obstetrics (FIGO). After maximal cytoreductive surgery, these patients received six courses of combination chemotherapy with carboplatin and cyclophosphamide. After completing chemotherapy, a second-look laparotomy was performed. Only those patients who had no obvious tumour or only minimal disease (lesions ≤1 cm) at the second-look laparotomy were included in the study.

Group 2 comprised 42 patients who had a radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection for (FIGO) Stage IB or IIA carcinoma of the uterine cervix and who were in complete remission for at least 9 months after surgery.

Group 3 comprised 14 patients (13 men and one woman) who underwent aortic surgery. All had either endarterectomy, bypass grafting for atherosclerotic occlusive disease or aortic replacement for aneurysmal disease.

In groups 1 and 2, the postoperative serum CA 125 levels were assayed daily during the first 2 weeks and then once a week for a further 5 weeks in group 1 (patients with ovarian cancer) or a further 10 weeks in group 2 (patients with cervical cancer).

In group 3 (aortic surgery) serum CA 125 levels were assayed on two occasions during the first post-operative week, and on three further occasions, during week 2, weeks 3–7 and weeks 8–12.

CA 125 immunoassay

Serum CA 125 levels were measured using a solid phase enzyme immunoassay (Abbott Laboratories, Chicago, USA) (Shaw *et al.* 1986). In 34 different assays, coefficients of variation of 10·2 and 8·9% were found at levels of 20 and 166 U/ml, respectively. All serum values ≤16 U/ml were regarded as normal. This cut-off represents the 95th centile in a population of healthy premenopausal women and is comparable to a level of 30 U/ml when measured using a radioimmunoassay (Pittaway *et al.* 1988).

Statistical analysis

We selected 42 patients (22 in group 1, 15 in group 2 and five in group 3) who had complete serial CA 125 measurements.

In these 42 patients, the analysis of variance was applied to the pretreatment serum CA 125 value, the mean serum CA 125 value on days 1, 2 and 3 and to the mean serum CA 125 concentration during the second postoperative week. Because the distribution of the serum CA 125 values was skewed, the analysis required logarithmic transformation.

Results

The mean serial serum CA 125 values are shown in Figs. 1 and 2. In all three groups, increasing serum CA 125 concentrations were noted after abdominal surgery. Elevated serum CA 125 levels were observed in 24 of the 28 patients (86%) in group 1, in 36 of the 42 (86%) in group 2 and in nine of the 14 patients (64%) in group 3. The highest serum CA 125 levels were found between 5 and 14 days after surgery. The mean level during the second week after surgery was statistically significantly higher than the normal pre-operative level (analysis of variance; $P<0{\cdot}0005$). The highest levels found in each of the three groups were 194 U/ml on day 9, 336 U/ml on day 13 and 215 U/ml on day 7 in groups 1, 2 and 3 respectively. There were no significant differences in serum marker trends between the three groups.

The elevated serum CA 125 concentrations gradually returned to the normal range between 3 and 4 weeks after surgery. Two months after surgery, the serum CA 125 levels were ≤16 U/ml in 69 out of the 72 patients (96%).

Discussion

This study shows that a postoperative rise in the

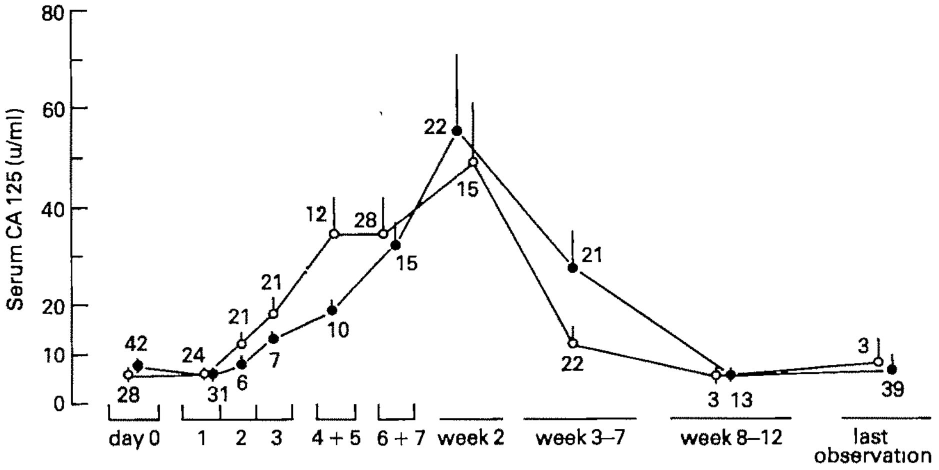

Fig. 1. Serial serum CA 125 levels before (day 0) and after abdominal surgery for gynaecological malignancy. Open circles. mean serum CA 125 levels before and after second-look laparotomy in 28 patients treated for ovarian cancer Closed circles: mean serum CA 125 levels before and after radical hysterectomy in 42 patients for Stage IB or IIA cervical cancer. The bars represent ±SEM values; the number of observations at each mean point are shown

serum CA 125 concentration is a common phenomenon following abdominal surgery, irrespective of sex, the primary diagnosis, or the type of operation. As a consequence, the use of CA 125 as a tumour marker in the early postoperative period is of only limited value.

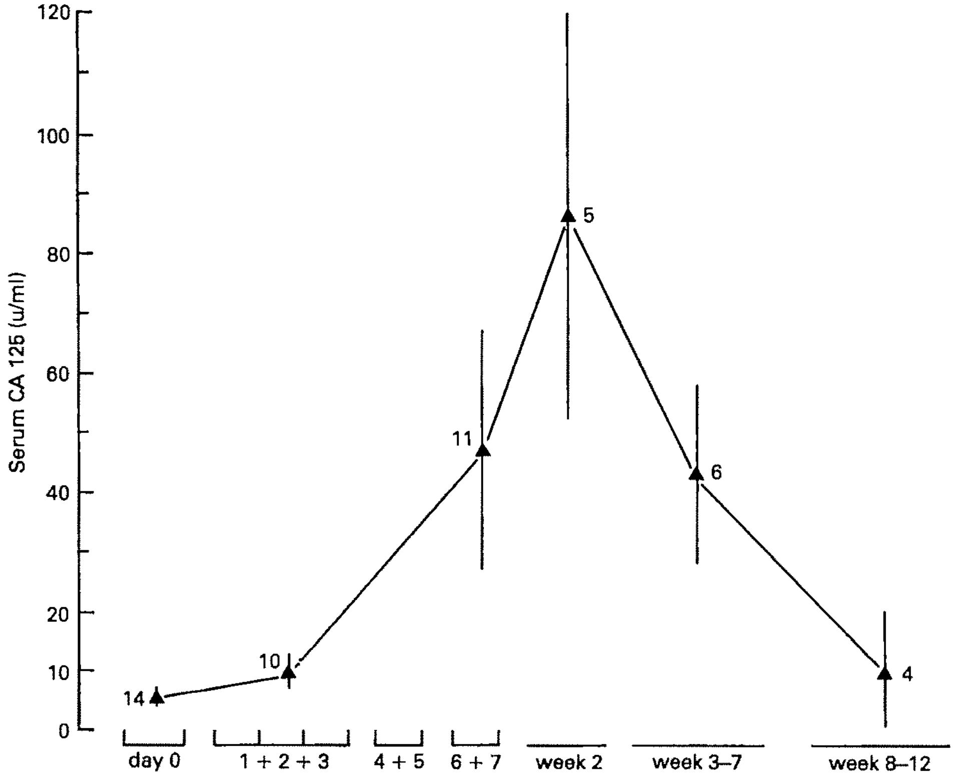

Fig. 2. Mean serum CA 125 levels before (day 0) and after aortic surgery in 14 patients (13 men and one woman). The bars represent the ±SEM values and the number of observations at each mean point are shown.

An increased CA 125 concentration in peritoneal lavage fluid (Redman *et al.* 1988) and in postoperative serum samples (Talbot *et al.* 1989) has been reported previously. Redman *et al.* (1988) did not observe an increase in serum CA 125, but they studied only six patients with a follow-up of 5 days. In agreement with our findings, Talbot *et al.* (1989) did note rising serum CA 125 levels following abdominal surgery in a miscellaneous group of patients who had normal pre-operative serum CA 125 values. However six patients with ovarian cancer reported by Talbot *et al.* (1989) showed a prompt decline in serum CA 125 after laparotomy; they all had elevated serum CA 125 levels before the operation and the decrease in serum CA 125 can probably be attributed to the removal of the primary antigen-shedding tumour, thus masking the effect of the laparotomy.

The patients with ovarian cancer included in our study had normal pre-operative serum CA 125 levels and no or only minimal disease at second-look laparotomy. Most of them (86%) showed a rise in serum CA 125 after surgery. Although this increase was only small compared with levels found in patients with tumours, but it may cause a troublesome differential diagnostic problem.

Taken together with our findings in groups 2 and 3 it is likely that the postoperative increase in serum CA 125 is of extra-tumoural origin The only shared factor among the three groups was an abdominal operation causing major trauma to the peritoneum.

Normal mesothelial cells on the peritoneal surface either stain only faintly or not at all when incubated with the monoclonal antibody OC 125, but reactive mesothelial cells show an intense positive reaction (Fleuren 1987). Clinically, a strong relation has been found between the degree of inflammatory peritoneal involvement and the serum CA 125 level in patients with acute salpingitis, confirmed at laparoscopy (Duk *et al.*, 1989*b*). Abdominal surgery may also induce shedding of the antigen by reactive mesothelial cells. Lymphatic drainage of peritoneal fluid, in combination with leakage of the antigen into the circulation after impairment of the peritoneal barrier, may subsequently result in an increase in the serum CA 125 concentration.

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Haemostatic changes during continuous oestradiol-progestogen treatment of postmenopausal women

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Summary. To identify changes in haemostatic balance during continuous oestradiol-progestogen treatment, 60 postmenopausal women with climacteric complaints, mean age 55·4 years (range 44–68) were randomly allocated to receive one of four hormone replacement regimens for one year. All four formulations were administered daily and continuously, each contained 2 mg of 17 β-oestradiol in combination with either norethisterone acetate, 1 mg (group A) or 0·5 mg (group B) or megestrol acetate, 5 mg (group C) or 2·5 mg (group D). No significant changes occurred during treatment within or between the groups in platelet count, fibrinogen and 2-antiplasmin. Activated partial thromboplastin time was shortened (P<0·05) in group D and a decline in factor VII activity and antigen (P<0·001) and in ATIII activity (P<0·05) was noted in group A. Protein C tended to decline in all treatment groups but statistically significant changes were noted only in groups A and C. Two women developed crural thrombosis during the observation period.

Climacteric complaints in postmenopausal women can usually be improved with oestrogen treatment (Campbell & Whitehead 1977). Furthermore, post menopausal osteoporosis in women is a serious complication of ageing. Prophylactic oestrogen treatment can prevent osteoporotic fractures after the menopause as well as diminish cardiovascular disease. However, long-term treatment is required to obtain benefits in bone mass preservation and prophylaxis against coronary heart disease (Lindsay *et al.* 1976; Lindberg *et al.* 1989). To minimize the risk of oestrogen-induced endometrial hyperplasia, progestogens should be added (Persson *et al.* 1989; Whitehead *et al.* 1981). Continuous oestradiol-progestogen treatment has been reported to produce atrophy of the endometrium and to minimize uterine bleeding in most women (Sporrong *et al.* 1988), and the amenorrhea during hormone replacement therapy (HRT) is preferred by most postmenopausal women (Hahn *et al.* 1984)

Thromboembolic disease is one of the most serious complications of oestrogen treatment and an increased incidence has been reported in oral contraceptive users (Bottiger & Westerholm 1971). During oestrogen treatment the haemostatic balance may be changed towards hypercoagulability. An increase of several blood coagulation factors and also a reduction of blood coagulation inhibitor capacity have been found (Henrikson *et al.* 1986; Lindberg *et al.* 1989;

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Gilabert *et al.* 1988). Contradictory results on fibrinolysis and enhanced platelet activity during oestrogen therapy have been reported (Jespersen 1987; Campagnoli *et al.* 1981). Variable results in blood coagulation, fibrinolysis and platelet function have also been reported in response to different oestrogens administered (Henriksson *et al.* 1986; Lagrelius *et al.* 1979, Coope *et al.* 1975; Poller *et al.* 1977). The most pronounced changes have been reported during treatment with ethinyloestradiol Few data have been produced on possible effects of progestogens on blood coagulation and on the fibrinolytic system (Conard & Samama 1983). The present study was conducted to assess the haemostatic balance during long-term continuous oestradiol-progestogen treatment.

Subjects and methods

Sixty women with climacteric complaints, attending our outpatient clinic, mean age 55·4 years (range 44–68) were included in this double-blind trial, they were randomly allocated by a randomization code to receive one of four hormone replacement regimens. No data were found before the study to reveal possible differences between progestogens in their effects on haemostatic variables, accordingly the present number of patients chosen were based upon known differences in the effects on high density lipoprotein (HDL)-cholesterol exerted by progestogens derivations of 19-nortestosterone and 17-hydroxyprogesterone. The randomization code was kept by an independent source and was not broken until completion of the study. All women were at least one year postmenopausal and the mean postmenopausal period did not differ between the four groups, 5·6 (SD 4·0) years All the women were treated for one year with a continuous oestradiol-progestogen regimen consisting of 2 mg 17-β-oestradiol taken daily in combination with either norethisterone acetate (NETA), 1 mg (group A) or 0·5 mg (group B) or megestrol acetate, 5 mg (group C) or 2·5 mg (group D). No hormone treatment had been given for at least six weeks before the study and they received no other medication except for anticoagulants in the women with thromboembolic disease. About 20% of the women were smokers and they were equally distributed among the different treatment groups. Twelve women stopped treatment during the study: one in group A, five in group B, four in group C and two in group D. Seven women stopped treatment because of bleeding disturbances.

Approval of the study was obtained from the university ethics committee All the women gave their informed written consent.

Methods

Samples were obtained by venepuncture between 0730 hours and 0900 hours after an overnight fast and after at least 15 min rest in the laboratory Samples were collected twice before treatment, with at least one week interval, and after 1, 4 and 12 months of each treatment regimen. The blood was allowed to flow freely into test tubes containing 0·13 M sodium citrate, and it was gently mixed and centrifuged at 2000 g for 20 min. Plasma was aspirated off and stored at −70°C in poly-propylene test tubes. All analyses were performed in duplicate or triplicate. Reference plasma were prepared from 20 healthy men and women, age 20–60 years.

Platelet counts used an automatic counter (ref. value 150–350 × 10^9). Activated partial thromboplastin time (APTT) was determined according to the manufacturer's instruction (General Diagnostics, New Jersey, U.S.A.) (ref. value 30–42s). The difference between the patient's value and the reference value was calculated and used for comparison between the different groups.

Fibrinogen was determined as fibrin according to Nilsson & Olow (1962) (ref value 2–4 g/l). Von Willebrand factor antigen (vWF:Ag) was analysed by an electroimmunoassay (ref. value 50–150% of normal) (Lindberg *et al* 1989).

Factor VII clotting activity was measured with a method using factor FVII deficient plasma, and performed on Coag A Mate X-2 from General Diagnostics, New Jersey, USA (ref. value 70–130% of normal). Additionally the factor VII amidolytic activity was analysed using the chromogenic substrate S-2222 (Kabi Vitrum Diagnostica, Molndal, Sweden) (Osvaldsson *et al.* 1985), (ref. value 50–120%). Factor VII antigen was determined by an Elisa technique (Lindberg *et al.* 1989), (ref. value 70–130% of normal).

Protein C was measured with an ELISA technique (Boehringer Mannheim Diagnostica, West Germany) (ref. value 70–130%). Antithrombin III (ATIII) activity was analysed using the chromogenic substrate S-2238 (Kabi Vitrum AB, Sweden) with bovin thrombin as activator

(Lindberg *et al* 1989) (ref. value 80–120% of normal).

Plasminogen, α2-antiplasmin and plasminogen activator inhibitor activity were determined by using the chromogenic substrate S-2251 (Kabi Vitrum AB, Sweden) (Friberger *et al.* 1978; Nilsson *et al* 1987) (ref. values 70–130%, 84–116% and 0–26 AU/ml).

Statistics

Conventional methods were used for calculating the mean and the standard deviation. Student's *t*-test and the nonparametric Wilcoxon signed rank test were used to test changes within groups during treatment. Analysis of variance (general linear models procedure and Bonferoni (Dunn) *t*-test) was used to assess differences between groups in Factor VII. A value of $P<0·05$ was considered statistically significant.

Results

Before treatment no statistically significant differences were found between the four groups A, B, C and D, Table 1 showed their baseline values compared with reference values. No significant changes occurred during treatment within or between the groups in platelet count, fibrinogen and 2-antiplasmin. APTT was shortened ($P<0·05$) in group D after 1, 4 and 12 months of treatment. vWF:Ag levels decreased ($P<0·05$) after 1 month in group B.

A decline in FVII activity, measured with the method using FVII deficient plasma, was noted in group A. A transient decrease after 1 month was found in groups B and C. When FVII was analysed with the chromogenic substrate method lower values were found in group B after 4 and 12 months of treatment compared to the levels found with the method using FVII deficient plasma (Table 2).

The immunological analysis of factor VII confirmed the decrease in FVII-activity, but there was also an increase in factor VII level after 12 months of treatment in group D (Table 2). The mean ratio between activity and antigen was 1·2 (SD 0·3)

The activity of ATIII decreased significantly during treatment in group A and it was also lower, compared with pretreatment values, after 1 month in group C (Table 3). Protein C tended to decline in all the treatment groups. However, significant changes were noted only in group A and C (Table 3). A significant rise in plasminogen occurred in the treatment groups A and D after 1 month of treatment but later returned to baseline concentrations (Table 4) The level of PAI was unchanged in group A. In groups B, C, and D there were a transient decrease in PAI levels during the beginning of treatment (Table 4).

Table 1. Haemostatic variables before continuous oestrogen-progestogen treatment in 60 postmenopausal women*

Variable	Reference value*	Before treatment mean	(SD)
Platelet count (×10^9/l)	150–350	313	(60)
APTT(s)	30–42	−2·1	(3·5)†
Fibrinogen (g/l)	2–4	2·6	(0·5)
F VII-clotting (%)	70–130	134	(28)
F VII S-2222 (%)	50–120	124	(25)
vWF:Ag (%)	70–130	106	(19)
F VIII.Ag (%)	50–150	120	(47)
AT III(%)	80–120	106	(11)
Protein C (%)	70–130	114	(24)
Plasminogen (%)	70–130	105	(15)
PAI (AU/ml)	0–26	12 5	(9)
α2-antiplasmin (%)	84–116	103	(9)

APTT = activated partial thromboplastin time
vWF Ag = von Willebrand factor antigen
AT = antithrombin
PAI = plasminogen activator inhibitor
*Reference plasma was prepared from 20 healthy men and women †APTT was expressed as difference between reference plasma and the patients.

Table 2. Factor VII activity, mean±SD, measured with factor VII deficient plasma or chromogenic substrate S-2222 and factor VII measured immunologically before and during continuous 17 β-oestradiol, 2 mg and either norethisterone acetate 1 mg (group A) or 0·5 mg (group B) or megestrol acetatate 5 mg (group C) and 2·5 mg (group D)

Variable	Treatment group	Before treatment			1 month			4 months			12 months		
		mean	SD	*n*	mean	SD	*n*	mean	SD	*n*	mean	SD	*n*
FVII activity (% of normal)	A	133	28	15	99 ***	25	15	89 ***	24	15	99 ***	24	14
	B	134	32	15	118 *	36	14	124	33	10	115	27	9
	C	127	25	14	105 ***	21	14	112	35	13	115	24	11
	D	141	26	15	123	33	14	134	50	14	127	25	13
FVII activity S-2222 (% of normal)	A	117	26	15	94 **	19	15	92 ***	19	15	93 ***	20	14
	B	127	33	14	125	36	13	114 **	36	11	110 *	31	10
	C	123	25	15	114	23	13	121	29	12	114	24	11
	D	131	15	14	121	17	13	124	14	12	124	22	13
FVII-AG (% of normal)	A	110	19	15	85 ***	16	15	82 **	27	15	86 **	29	13
	B	105	20	15	99	25	14	97 *	23	11	91 **	24	10
	C	99	18	14	93	19	13	98	24	13	95	24	11
	D	107	16	13	95	23	13	102	15	13	113 **	23	13

* = $P<0{\cdot}05$. ** = $P<0{\cdot}01$ *** = $P<0{\cdot}001$

Analysis of variance, Bonferoni (Dunn) *t*-test, $P<0{\cdot}05$

Two women developed crural thrombosis during the treatment period. In one (treatment group C) a thrombosis was confirmed by phlebography after 5 months of therapy. The hormone therapy was discontinued and she was treated with heparin and dicumarol. vWF:Ag was increased in this patient and the APTT was short, 26 s compared with 30–42 s in normal reference plasma. The ATIII activity and the protein C levels were normal before the thromboembolic episode occurred. In another woman in group D a thrombosis was diagnosed 4 days after hip fracture surgery, which was performed after 3·5 months of treatment. Subcutaneous heparin and dihydroergotamine were given prophylactically during and after the operation. She was allowed to continue hormone medication. The deep vein thrombosis was diagnosed by phlebography. She was treated with heparin and dicumarol for 10 days. At that time the anticoagulant therapy was stopped because of bleeding complications. No measurable changes in blood coagulation or fibrinolysis indicating increased risk for thromboembolism were found before surgery.

Discussion

Before hormone treatment all variables, except for increased factor VII activity, were similar to values in the reference plasma. Factor VII has been reported previously to increase with age and to be higher in postmenopausal compared

Table 3. Percentage change in antithrombin III (AT III) activity and protein C levels before and during continuous oestrogen-progestogen treatment in postmenopausal women (see legend Table 2)

Variable	Treatment group	Before treatment			1 month			4 months			12 months		
		mean	SD	*n*	mean	SD	*n*	mean	SD	*n*	mean	SD	*n*
AT III (% of normal)	A	103	8	15	95 *	16	15	93 *	12	15	92 *	10	14
	B	103	13	15	100	19	14	92	15	10	94	15	10
	C	111	12	14	102 **	6	14	104	14	13	104	11	11
	D	107	9	15	102	13	14	100	9	14	97	9	13
Protein C (% of normal)	A	117	23	15	109	33	15	102 *	16	15	105 *	24	14
	B	114	37	15	110	38	14	110	42	10	101	30	10
	C	115	17	14	96 *	20	14	103	28	13	99	13	11
	D	112	16	15	108	22	14	103	26	14	103	27	13

* = $P<0{\cdot}05$ ** = $P<0{\cdot}01$

Table 4. Plasminogen (%) and plasminogen activator inhibitor activity (PAI) (arbitrary units) measured with the chromogenic substrate S-2251 before and during continuous oestrogen-progestogen treatment in postmenopausal women. (See legend Table 2)

	Treatment group	Before treatment			1 month			4 months			12 months		
		mean	SD	*n*	mean	SD	*n*	mean	SD	*n*	mean	SD	*n*
Plasminogen (% of normal)	A	107	11	15	123 ***	11	15	114	13	15	111	13	14
	B	107	14	15	113	22	14	103	14	10	117	14	9
	C	103	21	14	104	22	14	111	22	13	102	27	11
	D	104	12	15	115 *	10	14	115	19	14	119	19	13
PAI (AU/ml)	A	12	9	15	8	8	15	10	9	15	9	9	14
	B	13	10	15	9 *	8	13	7	7	11	12	20	10
	C	12	6	14	5 **	7	12	7 *	6	12	12	12	11
	D	12	12	15	8 *	10	13	7 *	6	12	13	11	13

* = $P<0{\cdot}05$. ** = $P<0{\cdot}01$. *** = $P<0{\cdot}001$.

with age-matched premenopausal women (Meade *et al.* 1983).

During the continuous oestradiol-progestogen treatment small changes were noted in blood coagulation and fibrinolysis. The most pronounced changes were found in the women treated with the highest dose of norethisterone acetate. The most striking result was the decrese of factor VII, which otherwise is reported to increase during oestrogen treatment (Jespersen 1987; Coope *et al.* 1975; Poller *et al.* 1977). All methods used showed the same magnitude of decrease. Thus an increase of the extrinsic pathway inhibitor, an inhibitor of the factor VII-tissue factor complex, seems less likely. The decrease of factor VII might be beneficial since high factor VII levels have been reported to be correlated with an increased incidence of ischaemic heart disease (Meade 1987). The lowest level of factor VII was found in the group of women given the highest dose of norethisterone acetate. The oestrogenic influence was probably counteracted by the progestogen component.

Hereditary ATIII deficiency is associated with a higher prevalence of thromboembolic complications (Egeberg 1965). Oestrogen treatment is known to decrease this major inhibitor of blood coagulation (Conard *et al.* 1983; Gilabert *et al.* 1988; Jespersen 1987). Reduction of ATIII was also found during therapy in the present study. The reduction was small, about 10% and most women had normal ATIII levels during treatment. However, such a change can be of importance if, before oestradiol-progestogen therapy, the woman already has an ATIII level close to the lower normal limit of ATIII-activity. Even protein C decreased during therapy in the same group of women. Hereditary deficiency of protein C has also been reported to be connected with an increased incidence of frequency of thromboembolic complications (Horellou *et al.* 1984). No statistically significant differences were found between the different treatment groups. Thus no convincing evidence for a progestogenic influence on these inhibitors could be recorded.

The oestradiol-progestogen therapy had slight influences on the measured fibrinolytic variables. A transient increase of plasminogen was found, which has been reported previously (Jespersen 1987). The α2-antiplasmin activity was unchanged and the PAI activity decreased slightly. This is not unfavourable as high levels of PAI have been reported to be associated with thromboembolic disease and ischaemic heart disease (Wiman *et al.* 1985, Hamsten *et al.* 1985).

One of the women with thromboembolism had increased levels of vWF:Ag and shortened APTT before the episode. These changes could be an expression of hypercoagulability and increased risk for thromboembolism. Therefore it is important to withdraw HRT before, or provide thrombosis prophylaxis during, major surgery and/or immobilization.

The continuous oestradiol-progestogen therapy caused small changes in the haemostatic variables measured, which seemed to be favourable for most postmenopausal women. However, whether small changes in haemostasis could contribute to an increased risk of thromboembolism in individual women is not known. The addition of a progestogen to the oestrogen therapy did not seem to induce unfavourable haemostatic changes. Changes in haemostasis may influence the development of cardiovascular diseases (Meade 1987). However, other variables such as lipids and carbohydrates require consideration when metabolic effects of steroids are assessed.

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Effects of isradipine, a new calcium antagonist, on maternal cardiovascular system and uterine activity in labour

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Summary. The effects of isradipine (a new calcium antagonist of the dihydropyridine type) on maternal blood pressure and heart rate, fetal heart rate, and uterine activity in labour were measured. Uterine activity was recorded by an intrauterine microtip transducer catheter connected to a fetal monitor. Isradipine was given as a slow injection in doses of 0·5 mg (10 women), 1 mg (11 women), and 1·5 mg (6 women). A reduction of systolic (6–16%) and diastolic (19–22%) blood pressure was seen, and concomitantly there was an increase in maternal (29–34%) and fetal (3–10%) heart rates. Reduction in uterine activity was not dose-related (maximum reduction 17%). Side effects (headache, palpitations) were minor and well tolerated. One woman in the high-dose group had a shortlasting episode of hypotension. The results suggest that isradipine given as a bolus dose decreases blood pressure in pregnant women with little effects on uterine activity and fetal heart rate.

The ability of calcium anatagonists to reduce peripheral vascular resistance has made them first-line alternatives in the treatment of essential hypertension (Frishman *et al.* 1988). This ability also makes them interesting alternatives in the treatment of hypertension in pregnancy. In patients with pregnancy-induced hypertension, maternal blood pressure was effectively reduced by single doses of nifedipine (Walters & Redman 1984) or nitrendipine (Allen *et al.* 1987). Apart from their vascular effects, calcium antagonists may also have a tocolytic action. Nifedipine effectively relaxed isolated myometrium *in vitro* and inhibited uterine activity in pregnant patients (Ulmsten *et al.* 1980; Forman *et al.* 1986). Postpartum uterine activity, both spontaneous and induced by oxytocin and prostaglandin $F_{2\alpha}$ was also inhibited by nifedipine (Forman *et al.* 1982).

Recent studies in sheep and monkeys have suggested potentially hazardous effects of nifedipine and nicardipine, such as fetal acidosis, hypoxaemia, decreased uterine blood flow and fetal arterial oxygen content (Harake *et al.* 1987, Ducsay *et al.* 1987). However, adverse effects on the utero-placental blood flow have not been found in other animal studies (Veille *et al.* 1986), nor in hypertensive human pregnancy (J. Allen, personal communication).

Isradipine is a new calcium anatagonist with a high selectivity for vascular smooth muscle as opposed to cardiac muscle (Hof *et al.* 1987).

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Although the drug is of dihydropyridine type its action on uterine smooth muscle seems to be different from that of other calcium antagonists of the same type. We have found that isradipine had much less inhibitory effect on postpartum uterine activity than nifedipine (Ingemarsson *et al.* 1989). The relation between vascular and uterine effects is of interest for an antihypertensive drug used in pregnancy.

The aim of this study was to investigate the effect of isradipine on uterine activity in women in spontaneous labour. The maternal and fetal cardiovascular effects and possible side effects were also studied.

Subjects and methods

The study was carried out in the labour ward at the National University Hospital, Singapore. A total of 27 healthy women in labour with uncomplicated term pregnancies and the fetus in cephalic presentation participated in the study. All had spontaneous uterine activity and were in the active phase of the first stage of labour with the cervix dilated at least 3 cm. The study was approved by the local ethics committee and all the participants gave their informed consent.

Uterine activity was recorded by a Gaeltec microtip transducer catheter connected to a fetal monitor. The catheter was introduced through the vagina and the cervix into the uterine cavity after rupture of the membranes. The insertion of the catheter gave the women no discomfort. The uterine activity was recorded for at least 30 min before the drug was administered (observation period) and thereafter for 90–120 min (test period). The frequency and amplitude of uterine contractions and uterine activity, quantitated on line as the active contraction area above the basal pressure in kilopascal/seconds *(kPas)* every 15 min were monitored. The uterine activity was calculated electronically by a uterine activity integrator module in a conventional fetal monitor (Sonicaid FM3R, Chichester, UK).

The maternal pulse rate and blood pressure (BP) were checked every 5 min during the observation period. During the first 30 min of the test period the maternal pulse and BP were checked every 3 min, thereafter every 5 min. The mean maternal pulse rate and BP for each 15-min period were calculated.

The drug was diluted with saline to 20 ml in a glass syringe and was given as a bolus injection during 5 min. No other drug was given to the women 24 h before the test. The women were allocated by random numbers to three treatment groups. These groups were comparable for age, weight and height. In the design of the study 12 women were planned to be recruited to the groups receiving 0·5 mg and 1·0 mg and six women for the 1·5 mg group. Three women had to be excluded from the analysis, one for rapid progress in labour and two for technical problems.

Isradipine 0·5 mg. Ten women (6 nulliparous, 4 parous) with a mean age of 25 years (range 19–36), a mean height of 155 cm (range 144–167) and a mean weight of 59·5 kg (range 50·5–73·1) were given 0·5 mg of isradipine. The mean cervical dilatation was 4·6 cm (range 3–7).

Isradipine 1·0 mg. Eleven women (8 nulliparous, 3 parous) with a mean age of 25 years (range 20–31), a mean height of 153 cm (range 142–159) and a mean weight of 61·2 kg (range 48–75) were given 1·0 mg isradipine. The mean cervical dilatation was 5·0 cm (range 3–7).

Isradipine 1·5 mg. Six women (3 nulliparous, 3 parous) with a mean age of 24·5 years (range 22–31), a mean height of 155 cm (range 146–161) and with a mean weight of 63 kg (58-72) were given 1·5 mg isradipine. The mean cervical dilatation was 4·0 cm (range 3–5).

Side effects of the drug such as vomiting, palpitations, tremor, flushing and substernal pain were recorded.

The results are given as mean (SD) values. Student's paired *t*-test was used for statistical assessment. For the calculations a computer and a NWA-Statpac program was used. P values $<0·05$ were considered significant.

Results

Maternal and fetal cardiovascular effects

Isradipine 0·5 mg. The systolic BP (all measurements included) decreased by a mean of 6% (from 115 to 108 mmHg) during the first 15-min period when the injection was given (Fig. 1). The mean of the lowest value of the systolic BP (mean minimum) during the same period was 101 mmHg. The diastolic BP decreased at the same time by a mean of 20% (from 79 to 63 mmHg) with a mean minimum of 55 mmHg (Fig. 2). The maternal heart rate (MHR) increased from a mean value of 79 to 102 beats/min (29%) with a mean maximum of 104 beats/min. The fetal heart rate (FHR) increased by 3% during a period of 15 to 45 min after isradipine was administered.

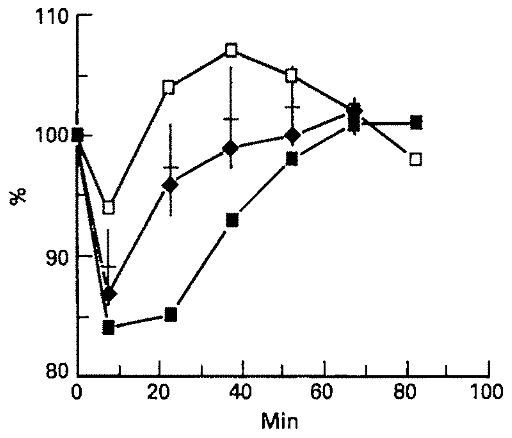

Fig. 1. Percentage change in systolic blood pressure after injection of 0·5 (□), 1·0 (◆) or 1·5 (■) mg of isradipine. The vertical lines show the mean change and 95% confidence intervals of all dose groups

Isradipine 1·0 mg. The systolic BP (all measurements included) decreased by 13%, from a mean of 122 to 106 mmHg. The mean of the lowest value of the systolic BP during the same period was 97 mmHg. The diastolic BP decreased by 19% from a mean of 77 to 63 mmHg with a mean minimum of 56 mmHg. The maximal effect was seen during the first 15 minutes of the test period. The MHR increased by 31% to 101 beats/min with a mean maximum of 103 beats/min. During the period of 15–45 min after isradipine was given the FHR increased by 8%.

Isradipine 1·5 mg. The systolic BP (all measurements included) dropped from a mean of 129 to 108 mmHg (16%) with a mean minimum of 99 mmHg. The diastolic BP decreased from a mean of 83 to 65 mmHg (22%), with a mean minimum of 69 mmHg. In this group the effect on the BP was more sustained (50–60 min) than in the other two groups. The MHR increased from 77 to 103 beats/min with a mean maximum of 107 beats/min (34%). The FHR increased by a mean of 10%

Changes in systolic and diastolic BP and MHR between preinjection values and values 15 min after the injection were statistically significant in all three groups. The drug effect was not proportional to the initial blood pressure but increased with increasing blood pressure. The mean effects on blood pressure are plotted with 95% confidence intervals in Figs. 1 and 2 for all three dose groups.

Effects on uterine activity

Uterine activity decreased in all three groups after the injection of isradipine with the maximum decrease during the first 15-min period (Table 1). The decrease was statistically significant ($P<0{\cdot}05$) in the 0·5 mg dose group. The uterine contractions gradually recovered to approximately the preinjection values within the test period of 75–90 min. The maximal decrease in uterine activity was similar in the 0·5 mg and 1·0 mg isradipine groups (17%).

The amplitude of contractions decreased, but not statistically significantly, in all three groups. This was balanced by an increase of the frequency

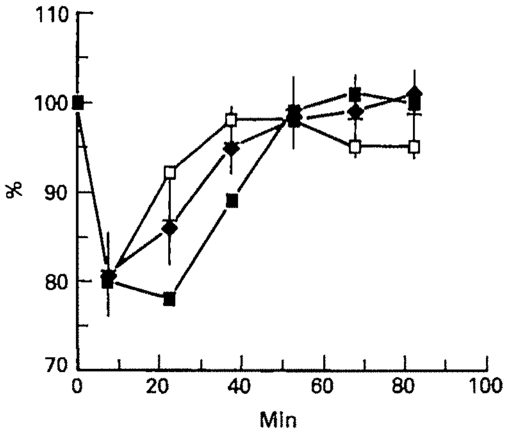

Fig. 2. Percentage change in diastolic blood pressure after injection of 0·5 (□), 1·0 (◆) or 1·5 (■) mg of isradipine. The vertical lines show the mean change and 95% confidence intervals of all dose groups

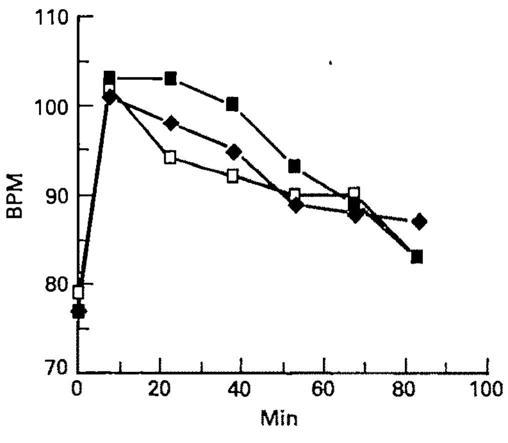

Fig. 3. Change in the maternal heart rate (MHR) after injection of 0·5 (□), 1·0 (◆) or 1·5 (■) mg of isradipine

Table 1. Uterine activity, amplitude and frequency of contractions after intravenous injection of 0·5, 1·0 or 1·5 mg of isradipine

Dosage	Variable	*n*	Mean change	SD	SEM	CI	*t*
0·5 mg	Activity	10	−227·3	247·4	78·2	−404·2 to 50·4	2·9*
	Amplitude		−5·8	10·1	3·2	−13·0 to 1·4	1·8
	Frequency		1·2	3·1	0·7	−0·4 to 3·5	1·8
1·0 mg	Activity	11	−240·8	425·4	128·3	−578·7 to 97·1	1·9
	Amplitude		−7·8	12·1	3·7	−13·4 to 1·9	2·1
	Frequency		2·2	1·8	0·6	−0·6 to 3·8	4·0*
1·5 mg	Activity	6	−142·3	267·1	109·0	−422·5 to 137·9	1·3
	Amplitude		−21·3	23·5	9·6	−46·0 to 3·4	2·2
	Frequency		3·3	1·8	0·7	1·5 to 5·1	4·6*

SD = Standard deviation. SEM = Standard error of the mean. CI = 95% confidence interval.
t = Student's paired *t*-test.* $P<0·05$
Changes in uterine activity is expressed in kPas, amplitude in mmHg and frequency in no./15 min.

of contractions ($P<0·05$ in the 1·0 mg and 1·5 mg dose groups). This trend was even more apparent in the 1·5 mg dose group, where a pronounced decrease of the amplitude and a concomitant sharp increase of the frequency of contractions was observed, leading to a minimal overall decrease in uterine activity.

Side effects

One woman in the 0·5 mg dose group and one in the 1·5 mg dose group experienced mild headache for about 10 min after the injection. Another woman (in the 1·0 mg dose group) reported palpitations for few minutes.

Hypotension (defined as a systolic BP <80 mmHg) occurred in one woman in the 1·5 mg dose group. The BP dropped from 120/80 to 80/60 for 7 min. Concomitantly, fetal bradycardia (70–90 beats/min) was recorded for 5 min but the FHR returned to normal thereafter. The baby was not distressed at birth.

All women had a normal delivery and all babies had Apgar scores of 9 or 10 at 1 and 5 min after birth. No postpartum complications were observed.

Discussion

Calcium antagonists produce vasodilatation in most vascular beds with reduction in peripheral vascular resistance and lowering of blood pressure. Their use in the treatment of essential hypertension is established (Frishman *et al.* 1988). As hypertension in pregnancy is associated with increased maternal placental vascular resistance, calcium antagonists may be suitable to treat pregnancy hypertension.

In this study the effects of isradipine in normotensive women in labour was studied after a bolus injection of the drug had been given. In this way hazardous effects of the drug on the maintenance of the maternal-fetal circulation with maternal hypotension and fetal heart rate changes would be detected. The results suggest that isradipine is a safe drug with regard to the utero-placental circulation. A dose-related reduction of the systolic and diastolic blood pressure occurred with a maximal effect during the first 15 min. The reduction was approximately twice as large for the diastolic blood pressure as for the systolic blood pressure. As expected when a vasodilator was given a concomitant increase in maternal heart rate was observed. This increase caused little discomfort. At the same time a small increase of the fetal heart rate was seen.

In one woman receiving the high dose (1·5 mg) of isradipine, a transient period of hypotension occurred. Simultaneously, fetal bradycardia (80 beats/min) was recorded for 5 min. However, the FHR recovered quickly and remained normal, the baby was born in good condition with normal Apgar scores and umbilical artery blood pH.

The effects of isradipine on spontaneous uterine activity were investigated with a microtip transducer inserted in the uterine cavity. With this technique the amplitude and the frequency of the contractions can be measured quantitatively. As the catheter was connected to a uterine activity integrator module in a conventional fetal monitor, an on line assessment of the uterine was obtained. We have used this model previously to study effects of beta-receptor antagonists and agonists on intrapartum uterine activity (Ingemarsson *et al.* 1985; Ingemarsson *et al.* 1987).

The results showed that isradipine, given as a bolus injection in doses of 0·5 mg, 1·0 mg and 1·5 mg, decreased the uterine activity in the first stage of labour, but the effect was small, transient and not dose-related (Table 1). In fact, the decrease was greater (17%) in the 0·5 mg and 1·0 mg dose groups than in the 1·5 mg group. The amplitude of contractions decreased in all three groups and the decrease was most pronounced in the 1·5 mg group (−43%), but a dose-related concomitant increase of the frequency (+60%) balanced most of the decrease in the amplitude. These findings contrast with those of our previous study (Ingemarsson *et al.* 1989) where we observed a moderate but well defined inhibition of postpartum uterine activity after isradipine administration. Comparisons of results on uterine activity obtained postpartum and intrapartum should apparently be made with caution. Our present results are also in contrast to those obtained with nifedipine, which had a pronounced inhibitory effect on uterine activity (Read & Wellby 1987). This difference in action is interesting as both drugs are of the dihydropyridine type. The relatively small effect of isradipine on uterine activity suggest that it should be of value in treating hypertension in labour.

Side effects of isradipine were mild; only three women reported headache or palpitations although comparatively high doses of the drug was used. All babies were in good condition at birth. Thus, the present results suggest that isradipine is a safe drug when given as a bolus injection to women in labour.

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Double survival despite cord entwinement in monoamniotic twins. Case report

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Case report

A 30-year-old woman was first seen at 13 weeks in her second pregnancy. Ultrasound at booking showed a twin pregnancy with expected date of delivery 16.6.89. She was admitted to hospital at 16 weeks gestation with vaginal bleeding. Repeat ultrasound indicated a low lying placenta. The vaginal blood loss settled after 3 days and she returned home with a diagnosis of threatened miscarriage. The remainder of her antenatal care was essentially normal except for a blood pressure of 140/90 mmHg in the last 2 weeks of pregnancy. At her last antenatal clinic appointment at 37 weeks gestation, an ultrasound scan showed twin I was cephalic and twin II a breech.

She was admitted on 26.5.89 at 37 weeks gestation with spontaneous rupture of membranes and draining clear amniotic fluid. Vaginal delivery occurred 35 min later, following right mediolateral episiotomy. Twin I was a face presentation—a girl weighing 2·85 kg with an Apgar score of 9 at 1 min. Following the birth of twin I, twin II was found to have a transverse lie and fetal bradycardia of 90 beats/min led to an emergency lower segment caesarean section. The second baby, also a girl, was born 24 min later. She weighed 2·76 kg and had Apgar scores of 2, 3, 4 and 7 at 1, 5, 10 and 15 min, respectively. At the time of the operation the placenta was observed to be anterior and encroaching on the lower segment of the uterus. Examination of the placenta (weight 1·3 kg) confirmed a monoamniotic twin pregnancy. The umbilical cords were entwined and appeared to be plaited (Figure 1) with 4 cm separating their vilamentous insertions into the placenta.

Twin I did well, apart from slight neonatal jaundice, and went home with her mother a week later. Twin II was kept in the Special Care Baby Unit for 10 days She developed hypocalcaemia which was corrected with calcium gluconate, 1 mmol/kg intravenously for 3 days. She was jittery and irritable and this was treated with mannitol and dexamethasone for 48 h and phenobarbitone for 5 days. A brain scan showed no abnormality.

Discussion

In monoamniotic twinning both twins occupy a common amniotic sac. According to McLeod & McCoy (1981) this condition was first described by Bocallini in 1612. It usually results from splitting of the germinal disc during development of the amnion in a uniovular twin pregnancy (Chapman 1974). More rarely it may be due to the breakdown of the normal amniotic partition between the two sacs (Dunnihoo and Harris 1966). Monochorial monoamniotic twins result from division of a single ovum between the 7th and 13th day of embryonic development. Division before day 7 results in diamniotic twins, after day 13 in monoamniotic conjoined twins. The exact incidence is unknown and ranges from one set of monoamniotic twins to every 165 twin deliveries (Raphael 1961) to one set of such twins to every 65 twin deliveries (Librach and Terrin 1957)

In monoamniotic twins there is a high fetal mortality, risk of fetal death being approxi-

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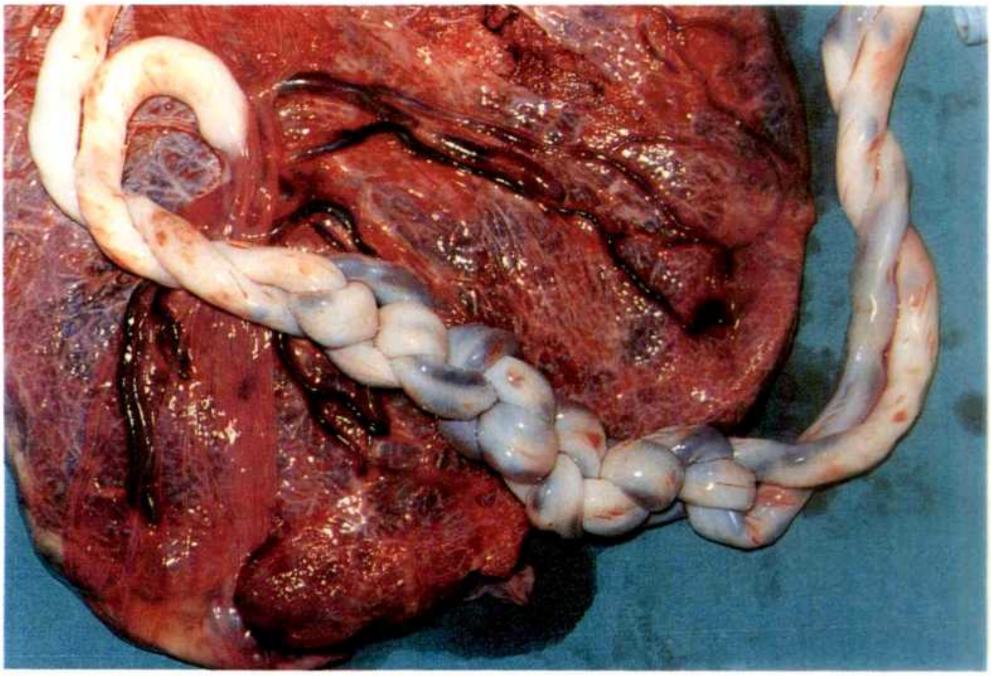

Fig. 1. Monoamniotic twin placenta showing plaited umbilical cords.

mately 40% (Tagawa 1974), due mainly to problems with the cords or the placenta. These include anaemia due to fetoplacental transfusion, occlusion of the umbilical cords by twisting or knotting—which may occur in 60% (Froglmann 1976) to 71% (Salerno 1959) and the cord of the second twin becoming entangled around the neck of the first twin.

The double survival which we managed to obtain is unusual. We suggest that whenever a multiple pregnancy is diagnosed, on ultrasound, an attempt should be made to identify a dividing amniotic membrane (Rodis *et al.* 1987). If this is absent the twins are monoamniotic and we recommend elective caesarean section. This is because the complications of fetal interlocking and cord entanglement, which may occur with vaginal delivery, will reduce the likelihood of double survival.

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Mucinous ascites associated with rupture of benign ovarian teratoma. Case report

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Case report

A 28-year-old woman had had intermittent pain in the left iliac fossa for 2 months. There had been no associated symptoms. She was admitted as an emergency because her pain had suddenly become much worse. She was afebrile and had mild tenderness without peritonism in the left iliac fossa. Her pain settled quickly and she was returned home the following day with arrangements for an outpatient pelvic ultrasound. The ultrasound examination was difficult to interpret but suggested a possible left ovarian cyst. A repeat ultrasound confirmed the presence of an irregular mass on the left side of the posterior pelvic wall, but the nature of the pathology remained uncertain Abdominal computerized X-ray tomography (CT scan) showed a cyst containing both low and high density areas with some calcification. There also appeared to be a considerable collection of fluid in the abdominal cavity that was divided by multiple septa (Figure 1). Retrospective review of the plain abdominal film at the time of admission showed some abnormal calcification but this was obscured by the sacrum.

Routine pre-operative blood investigations were normal, including alpha-fetoprotein. However, the tumour marker CA 125 was elevated at 84 000 U/l At laparotomy, 9 weeks after her initial presentation, almost 2 litres of thick, straw coloured, gelatinous 'marmalade' were removed from her peritoneal cavity. A large cyst (11 × 8 × 6cm) containing hair and sebaceous material originating from the left ovary had ruptured spontaneously into the peritoneal cavity. The peritoneal surfaces showed a fibrinous reaction. Culture of the peritoneal fluid was sterile and cytological examination showed mesothelial cells and histocytes. Histologically the resected specimen consisted of a cyst lined by mature squamous epithelium with dermal appendages and mucin-producing columnar epithelium The solid part of the cyst contained mature adipose tissue, bone and cartilage. The appearances were those of a mature cystic teratoma.

The patient made an uneventful post-operative recovery and left hospital after 7 days.

Comment

This case is of interest not only because of an unusual complication associated with rupture of a benign ovarian teratoma but also because it highlights some of the difficulties in the preoperative diagnosis of ovarian masses. Rupture of cystic teratomas is said to be rare because of the thickness of the cyst wall and only occurs in between 0·3% and 0.7% of patients. Rupture is often associated with another complication such as torsion, infection, trauma or malignancy, nevertheless, some ruptures remain unexplained. Rupture occurs either into a hollow viscus or into the peritoneal cavity. Rupture into other organs is a feature of very large tumours and these occur less frequently nowadays as a result of elective surgery for small lesions (Abitbol *et al* 1959; Carrusso *et al.* 1971; Pantoja *et al* 1975*a*; Stern *et al* 1981; Mitui *et al.* 1983). Intraperitoneal rupture of dermoid cysts has been associated with a number of different peritoneal reactions. Chronic leakage of contents can lead to a granulomatous peritonitis characterized by multiple small white peritoneal implants and dense adhesions. Alternatively, acute presen-

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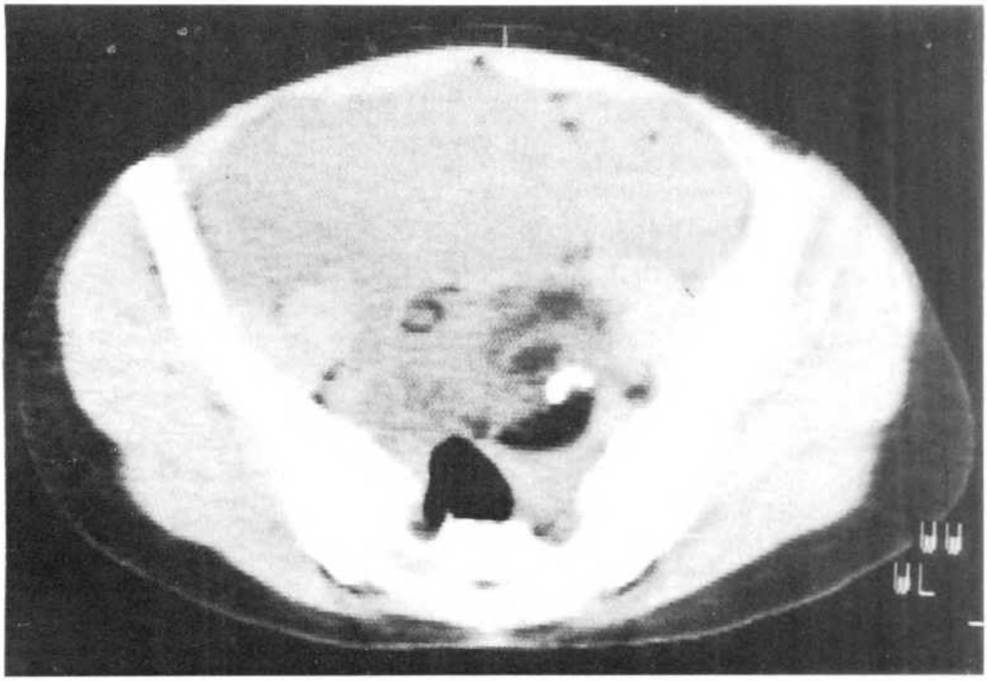

Fig. 1. C.T. scan through the pelvis showing the cystic area of the ovary together with an area of calcification. The fluid filled abdomen apparently divided by multiple septa is also seen.

tation with intraperitoneal rupture usually leads to a purulent peritonitis (Stern *et al.* 1981). Serous ascites has been described in association with rupture of a dermoid cyst that has undergone malignant change (Pantoja 1975b) and two cases have been reported when the peritoneum was filled with large quantities of sebaceous material (Abitbol *et al.* 1959; Graubard & Koller 1987). Mucinous ascites has not been described previously following rupture of a benign cystic teratoma.

It can be difficult to differentiate mucinous ascites from pseudomyxoma peritonei, a term used to describe a form of mucinous ascites associated with rupture of mucinous cystadenomas and cystadenocarcinomas of the ovary and benign or low grade malignant mucinous tumours of the appendix (Fernandez & Daly 1980; Sandenbergh & Woodruff 1977). There is still considerable debate as to what conditions should be classified as pseudomyxoma peritonei, in particular, as to whether the diagnosis should only be used in conjunction with malignant tumours or whether benign forms of the disease with prolonged survival should also be included (Fernandez & Daly 1980; Sandenberg & Woodruff 1977; Chejfec *et al.* 1986; Kochhar 1986). In common usage, the term can encompass any clinical entity associated with a mucinous ascites from any source (Limber *et al.* 1973; Chejfec *et al.* 1986; Kochhar 1986). Although our patient may be an example of pseudomyxoma peritonei no mucin producing cells were identified in the peritoneum.

It is uncertain how mucinous ascites is produced. One school of thought postulates that the rupture of a mucinous tumour releases cells that implant again elsewhere in the peritoneum. However, it has also been suggested that mucin production results from the irritant effect of a substance released from the ruptured cyst. This agent is thought to cause mucin production in mesothelial cells within the cyst and, when released into the peritoneal cavity, induces a similar reaction from peritoneal mesothelial cells (Sandenbergh & Woodruff 1977). This theory may explain the very large volume of mucinous fluid in our patient.

Despite the fact that mucinous ascites has not been described previously following the rupture of a dermoid cyst, it is explicable as up to 40% of dermoid cysts contain mucin producing elements (Fox & Langley 1979). However, both the rarity of rupture of dermoid cysts combined with the rarity of the occurrence of mucinous ascites makes our patient unusual.

This case highlights some of the problems associated with the pre-operative radiological diagnosis of ovarian teratomas. The simplest investigation is a plain abdominal film and if calcification is present the diagnosis is rarely in doubt. Nevertheless calcification can be very slight, completely absent or, as in our patient, largely obscured by superimposed bone (Lewis *et al.* 1982; Fleischer *et al.* 1978). Ultrasound is the most readily available diagnostic technique and cystic dermoids can be confidently diagnosed from a number of distinctive features including demonstration of a tooth, a fat/fluid level, a hair/fluid level, mural nodules (dermal plugs) or a highly reflective irregular solid component (Lewis *et al.* 1982; Quinn *et al.* 1985). The classical ultrasound feature is the 'tip of the iceberg' sign but this is demonstrated in about one-third of scans (Guttman 1977; Lewis *et al.* 1982). This feature results from a small hyperechoic area, typically calcification, casting an acoustic shadow (Guttman 1977; Quinn *et al.* 1985). Ultrasound can therefore detect pelvic masses but the appearance may be non-specific rather than diagnostic. The hair ball and sebum commonly found within cystic teratomas is also highly echogenic and can lead to errors in recognition of these tumours, due to an inability to delineate the boundaries of the mass (Fleischer *et al.* 1978). Repeat scans may also be required to differentiate the mass from either faeces or gas in the bowel (Guttman 1977). Undoubtedly one of the difficulties in our patient was the presence of mucinous ascites which resulted in a poor differentiation of the tissues due to a lack of change from one density of medium to another.

In the circumstances when both a plain radiograph and ultrasound have failed to yield a diagnosis of a pelvic mass, the investigation of choice is computerized tomography. The increased resolution and ability to demonstrate subtle differences in density provided by this technique will usually clarify the situation (Lewis *et al.* 1982). The increased availability of this investigation, allows the more accurate preoperative assessment of ovarian tumours.

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Non-immune hydrops in trisomy-18. Diagnosis by vaginosonography and chorionic villus sampling in the first trimester. Case report

JÁNOS SZABÓ, JÁNOS GELLÉN, GYORGY SZEMERE

Case report

An anxious, 36-year-old woman was referred for chorionic villus sampling (CVS) in her second pregnancy because of her age. The gestational age by menstrual dates was 10 weeks and 5 days and there was no report of any bleeding. A routine transvaginal sonogram showed an embryo of 31 mm crown rump length (equivalent to 6 days less than the gestational age), cardiac activity (136 beats/min), a dense yolk sac of 5·7 mm and a hypoechoic thin structure surrounding the head and the back of the embryo. The amniotic and chorionic membranes appeared normal. Transcervical sampling with a Trophocan cannula from the posterior chorion frondosum yielded 140 mg of chorionic villi at one cycle of aspiration. In our experience, samples of this size are not associated with poorer pregnancy outcome than smaller samples, and they are more convenient for laboratory investigations. The maternal serum alpha-fetoprotein (AFP) level was <5·0 µg/l before CVS and increased to 5·5 µg/l on the day after CVS.

Vaginosonography 7 days later confirmed the presence of a fetus with generalized hydrops, intrauterine growth retardation and a dense yolk sac (Figs. 1, 2). Cardiac activity and attenuated fetal movements were present.

An abnormal karyotype was suspected and chorionic villus material showed trisomy-18. After counselling, the couple asked for termination of the pregnancy and this was performed at 11 weeks gestation.

Discussion

With the introduction of chorionic villus sampling and transvaginal sonography, chromosomal and/or developmental errors of the fetus can be diagnosed during the first trimester of pregnancy (Szabó *et al.* 1986; Rottem *et al.* 1989; Editorial 1989).

An accumulation of fluid causing generalized oedema in the fetus is called nonimmune hydrops fetalis The reported prevalence ranges from 1 in 2500 to 1 in 3500 newborn infants (Macafee *et al.* 1970; Holzgreve *et al.* 1985). Thorough prenatal and postnatal investigation can explain 85% of these cases, leaving 15% labelled 'idiopathic' (Holzgreve *et al.* 1985)

An abnormal karyotype is one of the many different maternal, fetal and placental factors that have been shown to cause nonimmune hydrops fetalis.

Trisomy-18 (Edward's syndrome) is characterized by multiple congenital malformations in which virtually every organ system is affected. Developments in ultrasound imaging have made it possible to find pathognomic ultrasound signs for trisomy-18 fetuses. Intrauterine growth retardation, congenital heart disease, microcephaly, limb deformities etc. are known to be non-specific signs during the second and third trimester of gestation (Colley *et al.* 1987).

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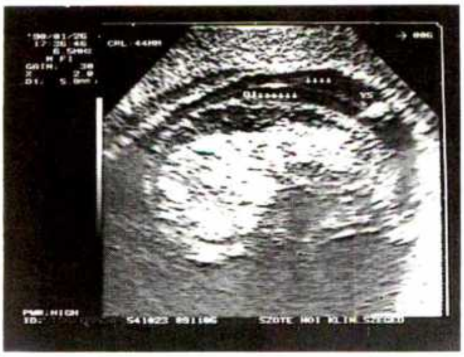

Fig. 1. Transvaginal logitudinal sonogram of the trisomy-18 fetus with nonimmune hydrops (crown rump length 44 mm). YS, dense yolk sac. Arrows indicate the hydrops and the amniotic sac.

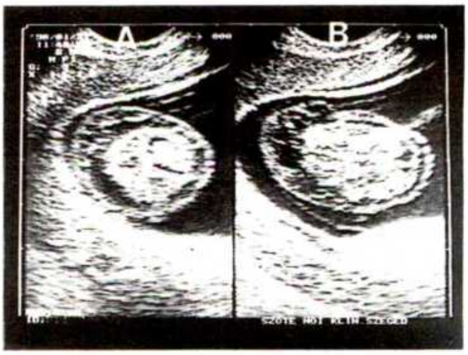

Fig. 2. Transvaginal transverse sonogram of the trisomy-18 fetus with nonimmune hydrops. Transverse section at the level of the chest (A) and at the head (B).

Choroid plexus cysts in the second trimester have recently been reported to be important ultrasound markers for trisomic-18 fetuses (Furness, 1987; FitzSimmons *et al.* 1989; Khouzam & Hooker, 1989; Ostlere *et al.* 1989).

As far as we are aware there have been no previous reports of first trimester diagnosis of trisomy-18 associated with hydrops fetalis.

Cytogenetic investigation may be informative when an embryo with nonimmune hydrops and/or smaller crown rump length and a dense yolk sac is seen during the first trimester. Prospective studies are now needed to determine the prevalence and significance of nonimmune hydrops fetalis in this very early stage of pregnancy.

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SHORT COMMUNICATIONS

Fetal macrosomia in potential diabetics with normal oral glucose tolerance: a case control study

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The clinical value of screening for gestational diabetes remains uncertain (Ales & Santini 1989) which is probably why screening programmes in various units range from the systematic to the haphazard. Many units use criteria of 'potential diabetes' to identify women for glucose tolerance testing and the schedule described by Nordlander *et al.* (1989) is typical and corresponds to our own. Screened women are those with: first degree relative with insulin-dependent diabetes; a previous baby with a birthweight >4000 g; a previous unexplained stillbirth or neonatal death; obesity or polyhydramnios in the current pregnancy.

Subjects and methods

Systematic screening for impaired glucose tolerance using the above criteria is conducted at the Northern General Hospital, Sheffield. Diagnostic criteria are those proposed by the World Health Organization (1980) using a 75 g oral glucose load. Women found to have impaired glucose tolerance and gestational diabetes are not reported here.

The present analysis includes 115 women identified as potential diabetics who had a negative oral glucose tolerance test (OGTT) at 28–32 weeks gestation. They were matched with 115 control women free from the stigmata of potential diabetes on a case control basis related to maternal age, parity, height, weight gain, and smoking habits (reference group). Capillary plasma glucose in the OGTT group was measured in a fully automated process using a glucose oxidase technique (YSM Model 23AM). Birthweight centiles were derived from the tables of Thompson *et al.* (1968). For comparison of two samples from two independent groups the Mann-Whitney *U*-test was used. To measure association between independent variables the Spearman rank correlation was used.

Results

Table 1 shows the maternal and infant data for all patients. Obesity was significantly more common in the OGTT group compared with the reference group ($P<0\cdot001$) Infants born in the OGTT group were significantly heavier than those in the reference group (3552 g compared with 3247 g; $P<0\cdot001$) and significantly more of them were large for gestational age (27% compared with 8%, $P<0\cdot001$)

When the women in the OGTT group were subdivided into those who were obese (Body mass index >1·6) and those who were not obese there was no significant difference in the mean birthweights between the two subgroups (obese 3576 g compared with 3509 g). There were somewhat more large-for-gestational age infants born in the obese group; the difference was not statistically significant (27% compared with 17%).

No correlation was found between maternal height, weight gain, age, parity, smoking habits and birthweight in any group.

Discussion

Endpoints of disordered glucose metabolism used by different units are difficult to compare but one consistent effect of excess maternal glucose transfer across the placenta is fetal macrosomia and, therefore, the reporting of

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Table 1. Maternal and neonatal characteristics in the study groups

	Potential diabetics			
Variables	All women (n=115)	Obese women (BM1>1·6) (n=73)	Non-obese women (n=42)	Reference group (n=115)
Maternal age (years)	26 (17–38)	26 (18–38)	25 (17–36)	26 (16–40)
Parity	1 (0– 5)	1 (0– 5)	1 (0– 5)	1 (0– 4)
Height (m)	1·63 (1·46–1·83)	1·62 (1·5–1 83)	1·63 (1·46–1·77)	1·61 (1·43–1·82)
Booking weight (kg)	77 (47–133)	84 (64–133)	65 (47–90)	57 (42–81)
BMI	1.78 (1 1–3·2)	1 95 (1 7–3·2)	1 5 (1·1–1·6)	1·3 (1·1–1·6)
Weight gain (kg)	10 (0–26)	10 (0–26)	11 (5–22)	11 (2–24)
Smokers	36 (31%)	23 (31%)	13 (31%)	24 (29%)
Neonatal				
Gestational age (days)	275 (217–294)	275 (238–294)	275 (217–294)	276 (224–294)
Birthweight (g)	3552 (1610–4875)	3576 (1610–4875)	3509 (2230–4360)	3247 (1630–4835)
LGA	27 (23%)	20 (27%)	7 (17%)	9 (8%)
SGA	3(3%)	2 (3%)	11 (3%)	11 (9%)
Preterm (<37 weeks)	7 (6%)	5 (7%)	2 (5%)	10 (9%)

Values are given a median (range) or n(%) as appropriate

Abbreviations: BMI=body-mass index calculated as $\frac{\text{(weight (kg)} \times 10^5}{\text{(height (cm)}^3}$ A value of >1·6 is considered 'obese'.

LGA=large-for-gestational age (>90th birthweight centile).
SGA=Small-for-gestational age (<10th birthweight centile).

macrosomia rates (birthweight above the 90th centile for gestational age) provides a basis for comparison (Gabbe *et al.* 1977) It is accepted that this is an indirect assessment of outcome and may be contaminated by the selection of women for diabetes screening who may be at increased risk of producing a macrosomic baby for other reasons. One clear association is with maternal obesity, and therefore by selecting women for diabetes screening on the basis of obesity, and using fetal macrosomia as an end-point we may be distorting the picture of diabetes associated morbidity by an element of self-fulfilling prophecy.

However, even non-obese women with other 'stigmata' of potential diabetes had larger babies than a comparison group although this trend was not significant with the small numbers used. Are the potential diabetic women producing an excess of macrosomic babies because of a metabolic disturbance, other than obesity, that is too subtle to be revealed by a glucose tolerance test? One possible explanation for this is that the glucose consumption of a fetus with established hyperinsulinaemia may be sufficient to 'correct' maternal post-load hyperglycaemia on glucose tolerance testing (Sutherland *et al.* 1978). This matter can only be resolved by studying fetal endpoints which will separate a hyperinsulinaemic macrosomic newborn from a non-hyperinsulinaemic constitutionally large infant Such studies might include detailed anthropometry, utilising ponderal index and skinfold thickness, cord blood insulin or c-peptide measurements (Macfarlane and Tsakalos 1985).

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Early identification of placenta praevia

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The position of the placenta, if 'low-lying' at 18 weeks amenorrhoea, is still thought by many to identify a sub-population of pregnant women who should be scanned again later in pregnancy to exclude placenta praevia. This policy commits a considerable amount of ultrasonic scanning time and often causes the woman both distress and inconvenience.

Because of the differences between published studies it was decided to review the frequency of placenta praevia in those women considered to have a low-lying placenta at the routine 18 week scan, and retrospectively to review the placental position at 18 weeks amenorrhoea in women with placenta praevia at term.

Subjects and methods

The study took place in the Royal Maternity Hospital, Belfast, between 1 January 1986 and 31 August 1986, 1490 routine ultrasonic scans at 18 weeks (range 16–20 weeks) were performed by medical staff trained in ultrasonic techniques. An Hitachi EUB25 ultrasound machine was used. All the women had a full urinary bladder.

Of the study population, 385 women (26%) had a low-lying placenta that appeared to reach or to over-lie the internal cervical os. Follow-up scan to determine placental position again was at the discretion of the consultant conducting the woman's antenatal care. Thus 270 of the 385 women were scanned again at approximately 32 weeks. If the placenta was still low, ultrasound scans were recorded every 2 weeks until the placenta was no longer in the lower uterine segment or the woman was delivered. The remaining women were only rescanned if there was a clinical suspicion of placenta praevia or if there was a coincidental indication for an ultrasonic scan.

A retrospective review of 30 women with placenta praevia, confirmed ultrasonically at or around the time of delivery, was also performed to identify the proportion that had been predicted by the 18 week scan. These patients were consecutive and occurred over 36 months.

Results

Of the 1490 scans performed at 18 weeks a low-lying placenta was recorded in 385. By the time of delivery there were seven women with placenta praevia, an incidence of 0·5% Only five of these had been considered low-lying at 18 weeks.

The retrospective review of the 30 women with confirmed placenta praevia was performed to see if the two pregnancies with placenta praevia that were not predicted at the 18-weeks scan were isolated occurrences. Only 18 (68%) of the 30 had been predicted at the 18 week scan, (range 16–20 weeks). Therefore as these were not isolated occurrences, Haynes Fourfold Format (Haynes 1981) was applied to the results obtained for the population of 1490 women, to determine the efficiency of the 18 week scan as a screening test for placenta praevia at term, the result is shown in Table 1.

Of the 385 women with a low-lying placenta at 18 weeks 270 were scanned again at 32 weeks. At this scan 14 women (5%) had placenta praevia but at term only five of the 14 (36%) had placenta praevia.

Discussion

Our results show that determination of placental

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Table 1. Haynes' Fourfold Format applied for the prediction of placenta praevia*

		At term/delivery		
		Normal placenta	Placenta praevia	
At 18 weeks	Normal palcenta	1103	2	1105
	Low-lying placenta	380	5	385
		1483	7	1490

Sensitivity 71·4%; specificity 74·4%, positive predictive value 1·3%; negative predictive value 99·8%
*From Haynes (1981).

position at 18 weeks gestation has little predictive value for placenta praevia in the final trimester. The high negative predictive value is distorted by the low incidence of placenta praevia and should not be taken to imply that scanning at 18 weeks excludes placenta praevia.

There are two recognized explanations for this: (i) placental migration and, (ii) observer error and marker misidentification. The concept of placental migration has been proposed in two forms by Sand (1977), and King (1973). Sand's theory depends on the differential growth patterns between the placenta and uterus carrying the placenta away from the internal cervical os as pregnancy progresses.

King's theory is of a dynamic placenta which, probably in seeking a better blood supply than the lower uterine segment can provide, mobilizes itself into the upper segment by a process of lower segment disattachment synchronous with the formation of new upper segment attachments. However, no pathological evidence for such a migration has been found.

Observer error and the resolution quality of the ultrasound machine are factors which it is not possible to allow for in this statistical assessment. However, all ultrasonographers were medically qualified and trained in ultrasonography and the same ultrasound machine was used throughout. The concept of marker misidentification is an attempt to understand and remove this source of error. It was first introduced by Zemlyn (1978), then Grannum & Hobbins (1983) and Bowie *et al.* (1978), but it was best explained by Artis *et al.* (1985) who cited two particular confounding factors, namely, (a) bladder fullness and (b) myometrial contractions.

The full urinary bladder is not only often erroneously thought to represent the lower uterine segment in the second trimester, but also can alter the shape of the cervix drawing the internal os up to give a false impression of proximity to the lowest margin of the placenta. Myometrial contractions in the late first and early second trimesters can similarly mislead the ultrasonographer.

To remove these factors, Commeau *et al.* (1983) used a scoring system for the 'degree' of lowness but were unable to correlate this with eventual placenta praevia. Artis *et al.* (1985) first repeated the scan with an empty bladder and then, if the placenta still appeared low, scanned the woman again after one hour, or the next day, to allow any myometrial contraction to resolve. With this protocol the incidence of low-lying placenta was reduced to 2·6%, however, none of the women had clinical placenta praevia. Townsend *et al.* (1986) were unable to reproduce these results and found the identification of the internal os difficult with an empty bladder. Artis *et al.* (1985) did not include a retrospective review of their women with placenta praevia to record the percentage which were not predicted by their protocol.

This lack of an accurate, easily reproducible test to predict placenta praevia has led Ruparelia & Chapman (1985) to abandon rescanning for placenta praevia unless clinically indicated. They record no adverse maternal or fetal effects.

Our findings, especially the high percentage of placenta praevia not predicted at 18 weeks, support this policy.

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Pipelle: a more acceptable technique for outpatient endometrial biopsy

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Endometrial sampling using a Vabra aspirator is an accepted alternative to formal dilatation and curettage (D & C) in the initial investigation of abnormal uterine bleeding (Grimes 1982).

In this study we investigated an alternative method of outpatient endometrial biopsy using a Pipelle sampler (Cornier 1984).

Subjects and methods

All premenopausal and perimenopausal women attending one consultant's gynaecology outpatient clinics were eligible for entry into the study if endometrial biopsy was indicated. A total of 104 women with a mean age of 41·6 years (range 21–54 years) entered the study.

The Pipelle consists of a piston sliding within a flexible polypropylene outer sheath with an external diameter of 3·1 mm (Fig. 1). Withdrawal of the piston creates a negative pressure and an endometrial biopsy is aspirated into the sheath.

After the biopsy was taken with the Pipelle sampler each woman was curettaged with a 3 mm diameter curbed tip Vabra curette. The samples were taken by one of two operators and were reported by one pathologist.

Results

Acceptability to the woman

Volsellum forceps were required to stabilise the cervix for both procedures in 40 women. Eighty-nine of the 104 women found both the procedures acceptable. Of the remaining 15 women, one complained of pain and two of discomfort with both procedures. The other 12 women reported that the procedure with the Pipelle was more acceptable than that with the Vabra. There were no complications of perforation, haemorrhage or infection from either procedure.

Acceptability to the clinician

In three women Vabra aspiration was successful

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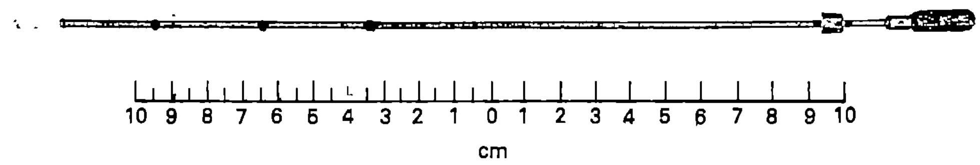

Fig. 1. Pipelle sampler

but Pipelle sampling failed because the flexible sheath was unable to negotiate a distorted cervix. In five women the Pipelle succeeded where attempts at Vabra aspiration failed; three due to failed insertion and two due to pain. Pipelle sampling was never abandoned due to pain. Both techniques failed in one woman due to distortion of the cervix. Paired biopsies were obtained from the remaining 95 women.

Acceptability to the pathologist

The Pipelle biopsies were smaller than the Vabra biopsies but they were equally suitable for histological processing and interpretation; 88 of the 98 Vabra biopsies and 88 of the 100 Pipelle biopsies provided adequate tissue.

Paired endometrial biopsies were suitable in 75 samples and histological diagnosis corresponded in 73 samples The spectrum of histology included normal endometrium ($n = 66$), cystic hyperplasia ($n = 3$), atypical glandular hyperplasia ($n = 2$), endometrial adenocarcinoma ($n = 1$) and endometritis ($n = 1$).

In one woman the Pipelle biopsy showed a benign endometrial polyp whereas the Vabra biopsy showed normal endometrium because the first sample removed the pathology.

In the only other samples in which the histological diagnoses differed the Pipelle biopsy showed normal endometrium; the Vabra biopsy and curettings from a subsequent curettage showed endometrial hyperplasia with cellular atypia. A subsequent hysterectomy revealed histological evidence of a benign endometrial polyp, which had been missed by the Pipelle, the Vabra and by formal dilatation and curettage (Stock *et al.* 1975).

Discussion

The use of outpatient endometrial sampling techniques reduces the number of hospital admissions and general anaesthetics with their attendant risks (MacKenzie & Bibby 1978). Cervical dilatation is not required and the risks of overcurettage and haemorrhage are reduced (Grimes 1982).

Pipelle sampling is more acceptable to the patient than Vabra aspiration and comparable to the Vabra for the clinician and pathologist. The Pipelle is portable making it suitable for use in a peripheral clinic. A Pipelle sampler is cheaper than a Vabra curette and there is no requirement for a motorized pump or initial capital outlay.

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CORRESPONDENCE

The obstetric forceps—are we using the appropriate tools?

Dear Sir,

We were interested to read the recent article by Hibbard & McKenna [*Br J Obstet Gynaecol* (1990) **97**, 374-380]. We were surprised at the wide variations in dimensions of forceps bearing the same name. The concern, however, ultimately relates to excessive and improper fetal head compression.

We would like to highlight here the features of a forceps model designed and described by Moolgaoker (1962). The taper wedge between the handles adjusts the grasp of the blades on the fetal head with a minimum of compression, irrespective of the size of the fetal head. Minor variations in the measurements of the blades resulting from hand forging (as opposed to drop forging) are compensated by the adjustability of the blades. Furthermore, it is notable that the author took detailed cephalic measurements of 1000 newborns before arriving at the measurements of the blades.

We find no technical difficulty in using these forceps both for rotational and non rotational deliveries.

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Change in ovarian arterial compliance during the human menstrual cycle assessed by Doppler ultrasound

Dear Sir,

Hata *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 163-166] studied ovarian artery pulsatility index (PI) in normal cycles in women. This method of investigating the arterial supply of the pelvic organs is attractive but has not been shown to be reproducible. Farquhar *et al.* (1989) showed that inter- and intra-observer variations in PI estimations in the uterine and ovarian circulation were unacceptably high.

The present authors have not presented any information regarding the reproducibility of their measurements, and indeed relied on a single measurement per observation in their study. Colour flow mapping might enhance the reproducibility of transabdominal pelvic Doppler measurements beyond that reported by Farquhar *et al.* (1989), but this needs to be demonstrated before the technique is introduced into clinical investigation.

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Caesarean section for the birth of the second twin

Dear Sir,

We read with interest the article by Samra *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 234-236] Their observation that 17 of the 22 caesarean sections performed to deliver the second twin occurred between 1700 and 0900 hours may reflect the need for experienced personnel at these deliveries. However, they offer no explanation as to why only two combined deliveries were necessary in the first 4 years of their review, during which time a total of 235 sets of twins were born. It would also be of interest to know the level of experience of the medical staff who were present when both twins were born vaginally and what time of day these deliveries occurred.

At the Rotunda Hospital, Dublin. 497 sets of twins were born between 1982 and 1988 (Table 1). In only 11 of these was a caesarean section necessary to deliver the second twin, an overall rate of 2·2% which compares favourably with the 4·3% of the Birmingham series. Our institution has long recognized the special needs of twin pregnancies (O'Connor *et al.* 1981), undoubtedly, careful supervision can prevent the increased use of caesarean section for the birth of second twins.

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Table 1. Frequency of caesarean section for twin pregnancies

		Caesarean sections	
Year	Twin deliveries	Both twins	Second twin
1982	66	9	0
1983	81	8	1
1984	66	14	2
1985	63	9	1
1986	80	20	4
1987	65	17	1
1988	76	16	2

Authors' reply

Dear Sir,

In our institution the rate of combination deliveries in the period 1980–83 was 0·9% (2/225) when the section rate for twin deliveries was 24% (53/225). For the period 1984–88, the rate of combination deliveries was 7% (20/285) when the caesarean section rate for twins was 46% (131/285).

This increasing use of caesarean section for twin pregnancies has been reported by others (Taylor, 1976; Cetrulo *et al.* 1980). In fact, on closer scrutiny, the Rotunda Hospital figures also show a similar trend, though not as marked as in our institution. For the period 1982–84 the Rotunda Hospital rate of combination deliveries was 1% (3/213), when the caesarean rate for twin pregnancies was 15% (31/213). For the period 1985–88, the rate of combination deliveries was 3% (8/284) when the caesarean section rate for twins was 22% (62/284).

In our institution one of the two combination deliveries during 1980–83 was performed between 0900 and 1700 hours and the other between 1700 and 0900 hours. The staffing levels have remained unchanged since 1980 but the use of caesarean section for delivery of twin pregnancies has increased appreciably. This trend has also been reported from other institutions. This may reflect a generalized trend, secondary to anxiety to ensure safe delivery of the precious fetuses which, in turn, leads to the trainee failing to gain experience in managing complicated vaginal deliveries, especially breech extraction of the second twin. Currently, in an attempt to break this vicious cycle, all twin deliveries in our institution are performed in the operating theatre with an experienced person present.

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BOOK REVIEWS

Motherhood and Mental Illness 2: Causes and Consequences edited by R. Kumar and I. F. Brockington. Wright, London, Boston, 1988, 294 pages with figures and tables, £42.50

The serious study of postpartum mental disorders has always been hampered by divisions within medicine which separate the safe birth of the child from how the mother as a person reacts to it. It is not an area, either, that has seen much of a co-operation between the different non-medical disciplines interested in motherhood. The contributions of psychologists, sociologists, anthropologists, social workers and so forth, though complementary in theory, are too often seen as providing competing models of explanation.

This collection of papers is a follow-up volume to one of the same name published in 1982 which coincided with the foundation of the Marcé Society. Its aim is to update knowledge and strengthen the methodological foundations of the study of postpartum mental illness. As such, it makes a valuable, though limited contribution. The value of the book lies in the comprehensiveness with which the various authors survey the field of psychiatrically-defined mental illness; its limitations derive from the same narrow field of vision. The book scans the particular landscape of women's distress and unhappiness after childbirth conceived of as a disease entity to be clinically managed and treated. However, and as Romito (1989) observed in a recent review, it remains an open and under-researched question as to how much of women's postpartum unhappiness it is appropriate and helpful to classify as mental illness. A related point is the somewhat artificial division between postpartum mental illness and mental illness/unhappiness throughout the whole period of motherhood. Unless maternal distress is generically/biologically linked to childbearing (which seems unlikely in view of the evidence discussed in this book), then aspects of women's social position as mothers surely deserve further investigation.

Ann Oakley

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Romito P. (1989) Unhappiness after Childbirth In *Effective Care in Pregnancy and Childbirth Vol. 2* (Chalmers I., Enkin M. & Kierse M. J. N. C., eds), Oxford University Press, Oxford, pp. 1433-1436.

Laser Surgery in Gynecology and Obstetrics. Second edition edited by William R. Keye Jr., Year Book Medical Publishers Inc, Chicago, London, Boca Raton, 1990, 278 pages with figures and tables, £59.00

In the four years since the first edition of Laser Surgery in Gynecology and Obstetrics was published there has been an enormous expansion in surgical laser techniques with the introduction of new delivery systems and new wavelengths. We therefore welcome the fact that Bud Keye's excellent book on gynaecological laser surgery has been enormously expanded and improved. The chapters on administration and organization of the laser unit by Dan Lundergan and on laser safety by Dan Martin are extremely helpful to gynaecologists who are starting to organize their own laser surgical units and the chapter on the future of lasers in gynaecology reflects the shifting emphasis from destruction of tissue by vaporization or photocoagulation to the more sophisticated aspects of photodynamic therapy with its potential applications in tumour therapy.

One of the big criticisms of the first edition of this book was the chapter on vulval surgery, particularly some of the photographs which illustrated a third degree burn which could easily have been achieved by diathermy. This has been entirely rectified by two brilliant chapters on HPV associated diseases of the lower genital tract and implications for the laser surgeon by Richard Reid, and laser therapy of the vagina and vulva by Cecil Wright. Although there have been few advances in laser treatment of the cervix, endometrial ablation or tubal microsurgery, the section on laser laparoscopy has been enormously expanded to reflect the wide interest in the use of lasers for an increasing number of laparascopic operations. This new edition includes four separate chapters covering the different lasers in current use, CO_2, Nd. YAG, Argon and KTP/532. This reflects the increasing popularity of laser laparoscopy in the United States where it is rapidly becoming the first line treatment of endometriosis. In this edition, Joe Feste from Houston has taken over the chapter on CO_2 laser laparoscopy and has provided an excellent description of the technique with comprehensive and detailed data based on his experience over the past 8 years. As with all new techniques there have been exaggerated claims of success by some of the pioneers but, with Dr Feste, the reader can be assured of an honest appraisal of the results that he has presented.

This new edition is a first class account of the state of the art in laser surgery and can be warmly recommended to all gynaecological laser surgeons. It should also be read by those who still employ the 'cut and thrust' of the surgical scalpel so that they understand what lasers have to offer their patients. Just as computers have become a routine part of everyday life, so the laser increasingly will become a routine surgical tool.

Chris Sutton

Books received some of which may be reviewed at a later date

Clinical Infection in Obstetrics and Gynaecology edited by Allan B. Maclean. Blackwell Scientific Publications, Oxford, Edinburgh, London, 1990, 392 pages with figures and tables £39.50

Basic Adolescent Gynecology: An Office Guide edited by Victor C. Strasburger. Urban & Schwarzenberg, Baltimore, Munich, 1990, 243 pages with figures and tables £39.25

Physics and Instrumentation of Diagnostic Medical Ultrasound by Peter Fish. John Wiley & Sons, Chichester, 1990, 250 pages with figures and tables £15.95

Pelvic Pain in Women: Diagnosis and Management edited by I. Rocker. Springer Verlag, Berlin, Heidelberg, 1990, 171 pages with figures and tables DM 120

Function and Sense of Radical Surgery in Gynecological and Mammary Cancerology in a Period of Biological Evolution—Controversies and Pitfalls by F. Uyttenbroeck. Peeters, Leuven, 1990, 661 pages fully illustrated. No price given

Current Therapy in Obstetrics and Gynecology—3 edited by E. J. Quilligan and F. P. Zuzpan. W. B. Saunders Co, Philadelphia, London, 1990, 426 pages with figures and tables £30

A Clinical Guide to the Care of Older Women by Richard L. Byyny and Leon Speroff. Williams and Wilkins, Baltimore, Hong Kong, London, 1990, 318 pages fully illustrated £43.50

Beyond Baby M: Ethical Issues in New Reproductive Techniques edited by Dianne M. Bartels, Reinhard Priester, Dorothy E. Vawter and Arthur L. Caplan. Humana Press, New Jersey, 1990, 288 pages £30.10

Monographs in Human Genetics Volume 13 Cholinesterase Genes: Multileveled Regulation edited by H. Soreq and H. Zakut. Karger, Basel, 1990, 116 pages with figures and tables SFr. 98. DM 117. £40.90

Contemporary Management of Urinary Incontinence edited by Peter H. C. Lim, P. G. Publishing, Singapore, 1990, 145 pages with figures and tables $35

Hormonal Contraception edited by Ronald L. Kleinman. International Planned Parenthood Federation, London, 1990, 122 pages $10.00 (or £5.00 in the UK only)

Community Participation in Maternal and Child Health/Family Planning Programmes edited by Susan B. Rifkin. World Health Organization, Geneva, 1990, 38 pages Sw fr. 9.50

Baillière's Clinical Obstetrics and Gynaecology. International Practice and Research. Volume 4, No 1. Antenatal Care March 1990 edited by M. H. Hall. Baillière Tindall, London, Philadelphia, 1990, pages 1-233 £22.50 single issue, £49.00 annual subscription

Baillière's Clinical Endocrinology and Metabolism. International Practice and Research Volume 4, No 2. Endocrinology of Pregnancy edited by S. Franks. Baillière Tindall, London, Philadelphia, pages 195-400. £22.50 single issue, £49 00 annual subscription

Unexplained Infertility: Basic and Clinical Aspects (Serono Symposia Publications Volume 62) edited by Giovanni Spera and Lucia Gnessi. Raven Press, New York, 1990, 315 pages with figures and tables $94.00

GIFT: Basic to Clinics (Serono Symposia Publications Volume 63) edited by G. L. Capitanio, R. H. Asch, L. De Cecco and S. Croce. Raven Press, New York, 1990, 474 pages with figures and tables $115.50

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COMMENTARIES

Effective Care in Pregnancy and Childbirth

It is rare for the editorial columns of a journal to draw attention to, or to review a book, but then it is also rare to have a book which merits such a notice. *Effective Care in Pregnancy and Childbirth,* edited by Chalmers, Enkin and Keirse, is probably the most important book in obstetrics to appear this century and its value to the profession will be profound and long lasting.

Twenty years ago that wise physician Richard Asher (1972) wrote:

'We always say "What is the treatment of this disease?" rather than "Is there a treatment for this disease?" Even the expression "effective treatment" is a quaint one . . . Logically we should not give treatment unless it is effective.'

He was driven to conclude that.

'It is better to believe in therapeutic nonsense, than openly to admit therapeutic bankruptcy . . . I find this one of the most uncomfortable concepts that logical reasoning leads me to. If you admit to yourself that the treatment you are giving is frankly inactive, you will inspire little confidence in your patients unless you happen to be a remarkably gifted actor, and the results of your treatment will be negligible. But if you believe fervently in your treatment, even though controlled tests show that it is quite useless, then your results are much better, your patients are much better, and your income is much better too. I believe this accounts for the remarkable success of some of the less gifted, but more credulous members of our profession, and also for the violent dislike of statistics and controlled tests which many fashionable and successful doctors are accustomed to display. It is an almost insoluble problem, and the majority of worthwhile doctors are driven to a compromise in which they muster enough genuine belief in their treatment to keep their patients happy and maintain their own self-respect, while preserving enough doubt to admit their inadequacy during transient bouts of uncomfortable honesty.'

For the practising clinician the problem is to preserve a balance between the certainty and self-confidence required to sustain clinical practice and the uncertainty and questioning attitude needed for the honest assessment of what he or she is doing. The practice of medicine is influenced by many things but there is good evidence that, in perinatal medicine, clinical decisions are influenced remarkably little by the results of research (Chalmers T. C. 1974; Richards 1975). That is a serious deficiency for the three main reasons pointed out by Chalmers & Sinclair (1985):

'Firstly, intervention in the perinatal period has had unintended and harmful consequences in the past: those practising perinatal medicine should be concerned to use research to help minimize such consequences . . . Secondly, in a field in which development is so rapid and diverse, it is important to distinguish real from apparent advances . . . The last of our reasons for wishing to see a closer relationship between perinatal research and perinatal practice is that perinatal medicine is expensive. If its practitioners wish to secure an appropriate share of the necessarily limited resources available, it is becoming clear that they will have to convince others that they can

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Effective Care in Pregnancy and Childbirth edited by I. Chalmers, M. Enkin & M. J. N. C. Keirse, Oxford University Press, 1989, 1520 pages in two volumes, numerous line illustrations and tables, £225.00

A Guide to Effective Care in Pregnancy and Childbirth edited by M. Enkin, M. J. N. C. Keirse & I. Chalmers, Oxford University Press, 1989, 376 pages, £9.95 paperback, £22.50 hardback

Oxford Database of Perinatal Trials edited by I. Chalmers, Oxford Electronic Publishing, Oxford University Press 1989, 5.25" or 3.5" disks and User Manual, £495 *deploy their allocation at least as effectively as competitors in other sections of the health and social services.'*

The situation must now be irrevocably changed by the publication of *Effective Care in Pregnancy and Childbirth.* Ninety-eight authors from 13 countries have assembled the available evidence about the effects of obstetric and midwifery care, with a major emphasis on randomized controlled trials. Studies published since 1950 in which there was a reasonable attempt to form a control group have been reviewed and included in the analyses when appropriate. The compilation is unique, not only because it represents such a comprehensive extract of published research but also because authors were approached for additional unpublished information, and because the results of trials that had not been published, often because of negative findings, were sought out and included when possible.

The effects of treatments are mostly shown as meta-analyses (Altman & Elbourne, 1988), with the results of every trial shown by odds ratios with confidence intervals; an overall odds ratio is calculated using the results from all of the trials. This is an instantly understandable statistical device that will certainly become commonplace and with which every educated obstetrician will wish to be familiar.

Chalmers and his colleagues have not written a textbook of obstetrics but, rather, have provided a critically assessed database that forms a foundation for current practice and future clinical research. The introductory chapters set out standards for assessing published clinical research and, by implication, the criteria that must be considered when the appropriateness of current practice is being reviewed and clinical research is planned. The clear definition of objectives and the accurate collection of data are fundamental, but research is inconclusive unless the study has the power to detect changes in treatment that are clinically important. Telling examples are quoted of well meaning clinicians initiating a treatment because current theory suggested that it would be beneficial and who found the treatment apparently successful in their personal uncontrolled series of patients. As a result, such a treatment became fashionable and widely used, only to be found to be valueless when properly designed controlled trials were performed. With good fortune, such treatments are harmless; but, occasionally, as with the stilboestrol therapy of women with a poor previous obstetric performance, not only was there no benefit but there were dire consequences for a small minority of the children treated in utero.

It is a sad reflection on clinical research that 160 pages are needed to review the methods for inducing labour but relatively few pages, scattered between the relevant chapters, on whether the induction of labour influences the outcome for mother or fetus. This is because the induction of labour often seems to be a solution to the uncertainty associated with clinical situations such as mild hypertension near term or a fetus that may be small for gestational age. Such inductions seem common sense, even though no clinical trials show that the outcome of the pregnancy is improved and there is the certainty that the outcome will be worsened for those few women who have a complication of induction that may lead to a caesarean section. There is, of course, pressure on young clinicians to perform research and a high induction rate naturally leads to research into methods of induction. Appropriate numbers of patients can be collected in the relatively short time that is available at this point in a young doctor's career. The much more important problem of whether induction of labour improves outcome requires participation by much greater numbers of pregnant women, because fetal and neonatal distress and perinatal mortality occur infrequently. Such research must be planned by experienced clinical research workers and, to be accomplished in a reasonable time, must be multicentred. The reader of *Effective Care in Pregnancy and Childbirth* is impressed by the small numbers of participants in most clinical studies and by the small power of the studies to detect important differences with confidence.

It is obviously impossible to offer a summary of the 1500 pages in these two volumes, with information ranging from the effect of social support in pregnancy, to monitoring in labour, and the techniques of delivery. There is an important emphasis on the women's experience of pregnancy and delivery; but much the greater part of the two volumes is concerned with clinical outcomes. As examples: corticosteroids given to women to promote pulmonary maturity in the immature fetus are shown to be valuable in almost all circumstances; the use of catgut to repair perineal trauma leads to more discomfort than alternative suture materials, has no advantages, and should be abandoned.

Clinical research must be a tightly disciplined science. There are many problems to solve. Modern methods of investigation are powerful and new pharmaceuticals have the promise of great value but also have a potential for harm. All clinical research must be properly planned so that there is a reasonable likelihood that a firm conclusion will be reached. In many situations there is no alternative to the randomized controlled trial and the proper use of statistical tests.

A summary of the analyses and conclusions presented in these two volumes is available in a paperback book entitled *A Guide to Effective Care in Pregnancy and Childbirth.* In addition the basic analyses are also being published in the *Oxford Database of Perinatal Trials* on computer disks, and these are updated at regular intervals. In this latter form the data are easily accessible and will include the most recent studies if a subscription is taken out for the departmental or library computer. All who propose to conduct clinical research must start their planning by referring to the appropriate section. Obstetrics will be changed forever, and for the better, by the appearance of these two volumes and by the innovative concept of a regularly updated electronic summary of all published trials in obstetrics.

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Andrology: a new sub-specialty

Infertility is a problem that is traditionally treated by the gynaecologists. However, infertility is often due to problems related to the male partner and this is a subject that is poorly understood by most gynaecologists. Few gynaecologists have had any training in urology and many do not understand the pathogenesis of reproductive failure in the male. As a consequence, couples are left without either a diagnosis or a prognosis and the treatment of infertility in men is poor. Without a diagnosis, there can be no rational or effective treatment. Andrology involves both the study and the treatment of disorders of the male genital tract and is a rapidly expanding branch of medical practice. The time has now come to consider it as a sub-specialty.

Andrology is fundamentally a surgical subject. However, it also comprises a mixture of surgery and medicine and, in particular, endocrinology. At present, andrology is frequently undertaken by practitioners on the fringe of the subject whose clinical skills are inadequate to encompass a proper understanding of the subject as a whole. Endocrinologists with an interest in gonadal function initiate treatment of male infertility without any training and little understanding of the surgical aspects of this subject. Likewise, there are some urologists who, although they attempt to treat male infertility, have no training at all in the extremely complex endocrinology that may be found in some men with reproductive failure.

At present patients tend to be treated by a 'committee' of clinicians. In this situation, responsibility for the overall care of the patient is frequently lost and confusion reigns, not only for the patients but also for their doctors.

For these reasons, the limits of andrological practice and its relation to other branches of medicine must be defined. The time has come to delineate the training required for this subject so that the andrologists of the future will be competent in their field. It is also time to examine the future of andrology as a sub-specialty in its own right.

The definition of andrology and its practice

The word 'andrology' suggests that the subject is fundamentally the male equivalent of gynaecology. If this were the case, the practice of andrology would involve the treatment of all the disorders of the entire genital tract in the male. As much of the urological and the genital tracts of the male serve both functions, the only difference between andrology and urology would be the exclusion from andrology of the disorders of the bladder and of the upper renal tracts. The specialty of andrology is thus best confined to the study and treatment of disorders of reproductive function—the management of male infertility. For example, andrology involves the diagnosis and management of disorders of testicular function in relation to reproductive failure but not the treatment of testicular torsion, testicular infection or testicular cancer Likewise, prostatitis and its role in the disruption of normal sperm function may be the province of the andrologist but the treatment of prostatic hypertrophy or prostatic cancer would, of course, remain within urology.

Included within the subject of andrology are all the surgical and endocrinological problems that can cause reproductive failure Andrology also encompasses the management of impotence and related penile disorders, the disturbances of ejaculation and the infertility-related disorders of the prostate and seminal vesicles.

Andrology includes the study of semen and of spermatozoa. Some scientists who study the pathology of semen and of spermatozoa have recently been calling themselves andrologists. However, embryologists do not call themselves gynaecologists and, for this reason, it is probably best if the title of andrologist is used to describe only the clinicians that are involved in the treatment of male infertility.

The role of the andrologist

The andrologist should be able to investigate and to treat infertility in the male. Surgical exploration makes up, as it does in the female, a very important part of the investigation of male infertility. Vasography, both antegrade and even retrograde, can be of great value diagnostically (Ford *et al.* 1982) and testicular biopsy may be very important in the differentiation of obstruction from other types of infertility in the male (Jequier *et al.* 1984). Cytoscopy together with the investigation of ejaculatory duct anomalies and of abnormalities of the bladder neck (Carson 1984) is also of value to the andrologist.

Although endocrine causes of infertility in the male were at one time thought to be relatively rare, such abnormalities may now be relatively common, especially amongst men with idiopathic oligozoospermia (Aiman & Griffin 1982). Recent work that is beginning to define the intragonadal hormones and their role in the control of gametogenesis makes an understanding of endocrinology essential to all clinicians involved in the treatment of male infertility.

Experience in the methods used in the analysis of both semen and seminal plasma is also essential to the andrologist. It is therefore important that the clinician is familiar with a wide variety of different laboratory techniques used in the assessment of seminal fluid in order to appreciate their limitations as well as importance in the investigation of infertility in the male.

The relation of andrology to both gynaecology and to female infertility

That infertility is the problem of a couple and not of an individual is a statement that is frequently made by clinicians in charge of infertility clinics. Indeed, a causative and an interactive relation between infertility in the male and in the female is well known. That the male fertility status may enhance female fertility and also exacerbate female infertility (and *vice versa*) is well described (Steinberger & Rodrigues-Rigau 1983). Thus the 'complete' andrologist should have a thorough understanding and also many of the surgical and medical skills of the gynaecologist. Such a clinician would have a clear understanding of the interaction between the male and female problems and would be able to provide the greatest therapeutic help to the infertile couple.

Another important reason why some gynaecological training is essential to the andrologist of today is that some form of assisted conception (IVF) is at present, and probably will continue to be, the only realistic treatment for male infertility. The small number of sperm that are needed to achieve an embryo in an IVF system (Yovich *et al.* 1985) can be processed in the laboratory to maximise the chances of fertilization (Yovich *et al.* 1990). Sperm can now also be obtained from the epididymis in men with obstructive azoospermia and successfully used in assisted conception systems (Patrizio *et al.* 1988, Jequier *et* *al.* 1990). The application of micromanipulation may result in fertilization and even pregnancy by immotile sperm (Laws-King *et al.* 1987). The modern andrologist must be able to use all these techniques within the context of assisted conception and, consequently, will need both a knowledge and some expertise in gynaecology.

The training of an andrologist

From the above comments, it is clear that the andrologist will need urological, endocrinological and gynaecological skills. As male infertility ceases to be an untreatable problem, the time has arrived to consider a programme of formal training in this subject.

As andrology requires surgical expertise, the basic training of an andrologist should be in either urology or gynaecology. If the basic training is urological then a period of 6–12 months should be spent in gynaecology. However, if the basic training is in gynaecology, a similar period of time should be spent in urology. Each potential andrologist should receive formal teaching in the reproductive endocrinology of both female and male gonadal function. Also needed is a period of training in the basic laboratory techniques such as hormone assays and semen analysis, that are used in the investigation of infertility; it is as important to appreciate the limitations of these procedures as it is to understand their applications.

As the application of assisted conception will continue to be so important in the treatment of male infertility, a system must be devised, within the private sector if necessary, for the training of andrologists in IVF and all the allied techniques of assisted reproduction. Such a training programme will integrate male and female infertility in the way that Steinberger and his colleagues have advocated so strongly for so long (Steinberger & Rodrigues-Rigau 1983).

This type of training programme will also provide the potential andrologist with a foundation for the research that is so badly needed for the future successful treatment of male reproductive failure. It should also rid us for ever of the 'amateur' andrologist whose personal references and clinical limitations are now tending to dictate treatment rather than the treatment being determined by the actual needs of the patient.

The training of an andrologist: an overview

Infertility in the male is an exciting new field for study. There is a great need for a better understanding of both the causation and the pathophysiology of infertility in the male. Male and female infertility are closely related and it could well be argued that any training programme should cover both aspects of infertility. The programme suggested above allows an individual this freedom. It also provides a proper foundation for research.

This training programme would need to be monitored. The treatment of infertility, especially when it involves the management of both men and women, crosses traditional demarcation lines between the Royal colleges. Monitoring such a training programme would require co-operation between the colleges but would probably be better overseen by experts from within a nationally based fertility society. However, with the agreement of the Royal colleges, it might even be possible to devise a system of continuing medical education in andrology. Of course, the exact manner in which such a teaching programme could be organized would depend upon the local traditions and constraints of each community or state.

The time has come to recognize the subject of andrology and to formalize the teaching of this subject. Treatment for male infertility is now available. The infertile male patient has the right to demand such treatment which should be of the highest possible standard. Only by correct training of the clinicians involved in this treatment can such a standard be reached.

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Non-surgical treatment of ectopic pregnancy

The incidence of ectopic pregnancy in Europe and the United States has shown a consistent increase over the last 20 years. Despite a corresponding fall in the death to case ratio over this time, the condition remains an important contributor to maternal mortality statistics.

For most patients, however, perhaps the most important consideration is the question of their future fertility. In the last century, when the diagnosis of ectopic pregnancy could be made only after the occurrence of catastrophic haemorrhage, salpingectomy, introduced by Lawson-Tait, was a life saving procedure. With the sophisticated diagnostic tests now available (hCG assay, vaginal ultrasound, diagnostic laparoscopy) it is possible to diagnose most ectopics before tubal rupture has occurred. Indeed these improved diagnostic techniques may have contributed in part to the apparent rise in incidence of the condition, with the recognition of some ectopics which would have previously undergone spontaneous resolution without detection.

There are unanswered questions about the true natural history of ectopic pregnancy and it is uncertain whether salpingectomy remains appropriate treatment for most patients.

Conservative tubal surgery (for example linear salpingostomy) can be performed either at laparotomy or laparoscopy. Laparoscopic techniques allow a short hospital stay, and appear to be applicable in most patients (Pouly *et al.* 1986), but they do require expertise and equipment that, as yet, are not universally available. Attention has also been focused on non-surgical means of dealing with the condition, with the aim of conserving the affected tube. In its most extreme form this approach involves simple observation of the patient in hospital with expectation of tubal miscarriage or spontaneous resorption of the pregnancy. Lund (1955) noted that approximately one third of the patients with suspected tubal pregnancy were able to avoid surgery, but for 60% of them this involved a stay in hospital of >1 month. It may become possible, however, to select patients in whom spontaneous resolution is likely on the basis of low or falling hCG and progesterone levels (Makinen *et al.* 1990).

Concern has been voiced that non intervention may result in chronic trophoblastic proliferation and continuing tubal damage, but the limited information provided by hysterosalpingography and repeat laparoscopy is reassuring on this point (Garcia *et al.* 1987).

Systemic chemotherapy was first used to treat an interstitial ectopic pregnancy by Tanaka *et al.* (1982) Methotrexate was chosen in view of its efficacy in the treatment of gestational trophoblastic disease. Several studies have since confirmed that methotrexate will produce resolution of ectopic pregnancy in most of the treated patients. Selection criteria usually require that the tube is intact and that the pregnancy is less than 3–4 cm in diameter. Treatment failure appears likely if fetal cardiac activity is seen on scan or if there are very high levels of hCG.

The main disadvantage of this form of treatment is the risk of systemic toxicity which can be lessened but not abolished by adding citrovorum rescue to the regimen.

In view of this problem, intratubal injection of methotrexate under ultrasound control was described by Feichtinger & Kemeter (1987). Injection under laparoscopic control may produce better results as the needle can be positioned more accurately. As little as 10 mg of methotrexate appears to be effective (Kojima *et al.* 1990) and, consequently, systemic toxicity is unlikely to be a problem.

As with systemic treatment, this method tends to be applied to small unruptured pregnancies and failures are more likely with high initial hCG values. Reinjection may be effective in this situation. Local injection of 0·5–1·5 mg of prostaglandin $F_{2\alpha}$ into the tube and corpus luteum has also been used with success (Lindblom *et al.* 1988) although cardiovascular side effects have been noted when higher doses are used (Egarter & Husslein 1988).

Preliminary work suggests that injection of 10–20 ml of hypertonic glucose is as effective as $PGF_{2\alpha}$ but does not produce the abdominal discomfort associated with the use of prostaglandins (Lang *et al.* 1989).

Whatever the chosen form of treatment, early recourse to diagnostic laparoscopy has much to commend it. The diagnosis of ectopic pregnancy can be confirmed, the presence of active bleeding or tubal rupture can be identified, the normality or otherwise of the rest of the pelvis can be assessed and laparoscopic surgery or guided tubal injection can be undertaken. Conservatism should not be confused with complacency.

Following *all* forms of conservative therapy, both medical and surgical, patients must be monitored with serial hCG measurement until the levels fall into single figures, although this can be undertaken on outpatients once values begin to decline.

Further treatment is essential if hCG values continue to rise to prevent the possibility of tubal rupture.

At present, although only 30–40% of patients meet selection criteria for injection methods, success rates are high and tubal patency is usually maintained. The risk of recurrent ectopic pregnancy is likely to be similar to the rate of 10–20% following conservative surgery.

Tubal conservation is no guarantee of future fertility. It is recognized that only about one third of women managed by traditional surgical methods will subsequently give birth to a live child. More encouraging figures have been reported after conservative surgery although the effect of patient selection should be taken into account.

It remains to be seen whether non-surgical treatment carries any advantage over conservative laparoscopic surgery both in the short and long term.

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Screening for viral and protozoal infections in pregnancy. A review

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As a result of widespread publicity in the lay press and on radio and television, antenatal clinics in the UK have recently been inundated with demands from healthy pregnant women that current serological screening for rubella, hepatitis B, and human immunodeficiency viruses in pregnancy be expanded to encompass two additional agents: cytomegalovirus (CMV) and the protozoan *Toxoplasma gondii.* Some clinicians have suggested that screening for a third infective agent, parvovirus B19, should also be included. The value of *T. gondii* and CMV screening has been both passionately supported and vigorously refuted in the medical press of this country (Joynson & Payne 1988; Ho-Yen *et al.* 1988; Salmon 1988; Editorial 1989*a*) and of the United States (McCabe & Remington 1988*a*; Thorpe *et al.* 1988; Yow 1989). To reach a dispassionate conclusion regarding the need to expand serological screening, we have reviewed the currently available laboratory and clinical data.

Established screening

Serological 'screening' of pregnant women for evidence of past or current infection with rubella is well-established. Non-immune women are offered active immunization post-partum and women who develop primary rubella during the first trimester should consider termination of pregnancy because of the high risk of congenital infection with consequent heart, eye and ear defects (Best & Banatvala 1987).

Selected antenatal screening for serological evidence of infection with two further viruses—human immunodeficiency virus (HIV) and hepatitis B virus (HBV)—has recently been introduced. Screening for HIV (dependent on informed consent) should be encouraged in women at increased risk of infection such as prostitutes, intravenous drug abusers, and the sexual partners of intravenous drug abusers, bisexual men, or men treated with blood clotting factors (European Study Group 1989). Seropositive women are candidates for termination of pregnancy, because pregnancy may accelerate progression to the acquired immune deficiency syndrome (AIDS) (Feinkind & Minkoff 1988). Moreover. the risk of HIV transmission from mother to fetus is at least 24% (European Collaborative Study 1988; Bradbeer 1989; Hira *et al* 1989; Blanche *et al.* 1989) and 20% of infected offspring develop AIDS in the first year of life. whilst the remainder develop the disease at a constant rate of 8% per year (Auger *et al.* 1988). Additional potential benefits of identifying maternal HIV infection include improving survival time by azidothymidine therapy (contraindicated in pregnancy) (Fischl *et al.* 1987, Editorial 1989*b*) and the quality of that survival by prompt treatment of opportunistic infection.

Women considered to be at risk of HBV infection (including the risk groups detailed for HIV infection, those with a recent personal or family history of jaundice, Caucasians from Southern and Eastern Europe and all ethnic groups other than Caucasian (Badenoch 1988)) are screened for hepatitis B surface antigen (HBsAg). Antigen-positive individuals undergo further testing for hepatitis B 'e' antigen (HBeAg) and antibody (anti-HBe). Transmission of HBV infection from HBeAg-positive or HBeAg- and anti-HBe-negative carrier mothers results in 70–90% of their offspring becoming chronic virus carriers (Ghendon 1987) Some 25–30% of these infants will eventually die from primary liver cancer. Most infants are infected peri-

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natally and thus transmission may be prevented by administration to the newborn of combined passive (hepatitis B immune globulin 200IU at birth) and active immunization (hepatitis B vaccine at birth, 1 and 6 months) (Ghendon 1987). This regimen fails to prevent infection in a few babies (5–10%) because either infection occurred *in utero* (Stevens *et al.* 1985) or the maternal blood contained very high levels of HBV DNA and therefore presumably of HBV (Lee *et al.* 1986). As almost all infants of anti-HBe-positive mothers either escape infection (90%) or develop only a transient asymptomatic infection, current UK guidelines (Polakoff & Vandervelde 1988) indicate that these infants do not require immunoprophylaxis.

This screening and intervention programme for HBV infection is under current review. Alter *et al.* (1989) suggest that 'at risk' pregnancies are missed because of the selective nature of the present antenatal screening programme, and there have been calls for universal HBV screening in pregnancy (Hoofnagle 1989). The policy which denies immunoprophylaxis to offspring of anti-HBe-positive women has also been questioned (Delaplane *et al.* 1983). Fulminant hepatitis has been recorded in children born to anti-HBe-positive women (Delaplane *et al.* 1983, Sinatra *et al.* 1982, Chang *et al* 1987), although in none of these instances was the presence of anti-HBe established antepartum. At least in Britain the risk of acute hepatitis B in infancy is probably less than 1 in 5000 for children born to HBV carriers (Polakoff & Vandervelde 1988).

Screening for cytomegalovirus infection

Two forms of CMV infection—primary in the previously uninfected, recurrent in the remainder—occur in pregnancy. Infants congenitally infected as a result of their mother experiencing primary CMV infection in pregnancy are more likely to have significant sequelae than are those infants infected after reactivated maternal infection (Stagno *et al.* 1982). The congenital defects produced by CMV include microcephaly, severe mental retardation, blindness or deafness (Freij & Sever 1988).

The absence or presence of CMV-specific IgG antibody in a preconception serum identifies women at risk of primary or recurrent infection. Approximately 50% of women of child-bearing age in the UK lack CMV-specific IgG antibody (Klapper, unpublished observations) as assayed by a sensitive radioimmunosorbent assay (Klapper *et al.* 1990). Yow (1988) recently argued that seronegative pregnant women should be identified and advised to avoid contact with potential sources of CMV, such as the saliva and urine of young children and the semen of adult males. Whilst this strategy may appear attractive it is clearly impracticable. Implementation requires that susceptible pregnant women are told to avoid kissing children on the lips, putting children's fingers into their mouths, and to abstain from sexual intercourse (Editorial 1989*a*). The use of high standards of personal hygiene by health care workers occupationally exposed to CMV is associated with a rate of primary CMV infection similar to that observed in control populations (Adler 1988; Jones *et al.* 1985; Pass & Hutto 1986) but this observation does not prove the protective efficacy of hygienic measures (Morris 1990). Even if careful personal hygiene protects hospital staff, extrapolation of this conclusion to women outside a closely supervised environment may be invalid (Morris 1990).

Although CMV vaccines are under active development (Plotkin 1985) no licensed product is yet available to protect against primary CMV infection. If seronegative women cannot be protected from infection, identifying them and labelling them as being 'at risk' will generate in them great—and for the most part, unnecessary—anxiety. Moreover, even if prevention of primary infection in pregnancy were possible CMV-induced congenital damage would not be completely abolished because damaged babies can be born following maternal recurrent infection (Alhfors *et al.* 1981, Rutter *et al.* 1985).

Transmission of infection may occur at all stages of pregnancy (Stagno *et al.* 1982) but the risk of severe congenital damage is probably higher when infection occurs in the first half of gestation (Stagno *et al.* 1986). Termination of pregnancies complicated by primary infection is therefore an apparently attractive alternative option (Editorial 1977). It has been suggested that detection of CMV-specific IgM antibody in maternal serum is diagnostic of primary infection during pregnancy (Griffiths *et al.* 1982). Primary CMV infection is almost always asymptomatic in pregnancy (Editorial 1989*a*) but pregnancies complicated by this infection could perhaps be detected by screening of all susceptible pregnant women for specific IgM antibody.

However, analysis of the antibody response during CMV infection and of the risk of CMV-induced congenital defects following maternal infection reveals that routine screening of pregnant women for primary infection would be counterproductive.

First, the detection of CMV-specific IgM antibody in maternal serum is not a precise marker of primary infection in pregnancy (Morris 1987). As CMV-specific IgM antibody occasionally persists for more than 4 months after primary infection, it may be impossible to determine whether an infection occurred during, or before, pregnancy. Furthermore, this antibody may be detected (albeit rarely) during recurrent infection. Second, in primary maternal infection the risk of mother-to-fetus transmission is 20–50% (Preece *et al.* 1983), and the risk of congenital damage in an infected fetus is 10% (Peckham & Logan 1988). Thus only about 1 in 30 of the pregnancies complicated by primary CMV infection results in the birth of a CMV-damaged baby. As there are about 600 000 live births per year in the UK and the frequency of primary infection is approximately 75 per 10 000 pregnancies (Griffiths & Baboonian 1984), 4350 potentially healthy babies would have to be aborted to prevent the birth of 150 congenitally damaged infants.

Prenatal confirmation of intrauterine infection by demonstration of fetal CMV-specific IgM antibody or detection of virus in amniotic fluid is of little value. Since the confirmation of intrauterine infection has little predictive value (1 in 10 risk of damage) the application of such invasive procedures must also be open to question.

Therapy with the anti-CMV drug ganciclovir is unsuitable for mothers with primary CMV infection. Ganciclovir (Hirsch & Kaplan 1990) is licensed *only* for treatment of severe CMV infection; it is fetotoxic, toxic to bone marrow and may cause permanent infertility in women. This narrow therapeutic-toxic dose ratio precludes its use when most babies of infected mothers develop normally.

Screening for *Toxoplasma gondii* infection

There are three distinct life forms of *Toxoplasma gondii*: the trophozoite or proliferative form, the tissue cyst and the oocyst. Toxoplasmosis is principally a zoonotic infection of felines though infection has been documented in almost all mammals and also in some birds (especially ground feeders). Man has been thought to acquire the infection either by consuming raw or undercooked meat containing tissue cysts or by ingestion of oocysts shed in cat faeces. Simple measures such as good personal hygiene and avoidance of raw or 'rare' meats have therefore been proposed to prevent infection. There is no vaccine.

Production of oocysts by *T. gondii* requires completion of a sexual reproduction cycle within intestinal cells. Trophozoites differentiate into micro-(male) and macro-(female) gametes and their subsequent fusion results in development of oocysts which are ultimately shed in faeces. Shedding of oocysts has thus far only been demonstrated for members of the Felidae, the domestic cat (Hutchinson *et al.* 1969; 1970) being first identified and now suggested as the definitive host even though cats probably only produce oocysts upon first encounter with the organism (i.e., as kittens) (Frenkel & Ruiz 1981; Menning 1989). The oocyst as shed in cat faeces is relatively hardy and can survive in soil for several months. With suitable moisture and oxygen content oocysts sporulate in the external environment to yield two oval sporocysts then four sporozoites all contained within the original cell wall Ingestion of the mature oocyst through contact with cat excreta, contact with soil through gardening and consumption of unwashed vegetables are considered to present a hazard of infection (Frenkel & Ruiz 1981; McCabe & Remington 1988*a*). However, various invertebrates (e.g., flies) may act as vectors for the mature oocyst through their habit of cophrophagy and subsequent contamination of other foodstuffs.

The commonest mode of spread to man has yet to be defined (Fleck & Kwantes 1980). The present emphasis on the domestic cat as the source of infection is probably too simplistic. If contact with cat faeces is the major route of transmission then high infection rates might be expected in young children (Bannister 1982) who are often in close contact with animals and are without regard for personal hygiene. Yet, the seroprevalence of *T. gondii* is extremely low in both school and pre-school children (Bannister 1982). The low seroprevalence in cat breeders (Woodruff *et al.* 1982) casts further doubt on the importance of cats in transmitting the infection.

The current UK seroprevalence in women of child-bearing age is not known, but it may have declined from the 14–35% that Fleck observed in 1969 (Fleck & Kwantes 1980) as it has in the United States (McCabe & Remington 1988*b*). This decline may be significant in relation to the risk of toxoplasmosis. Toxoplasma tissue cysts in meat are readily killed by freezing (Fleck & Kwantes 1980) and since 1969 both commercial and domestic freezing of meat before consumption has become commonplace. Determination of the current seroprevalence of toxoplasmosis may be of importance in defining the major route for acquisition of toxoplasma infection by humans and in properly assessing the risk of congenital toxoplasmosis.

Severe cases of congenital toxoplasmosis exhibit some or all of the tetrad symptoms described by Sabin (1941), namely chorioretinitis, cerebral calcification, hydrocephalus and mental subnormality. Mild cases may have localized retinal lesions which are unnoticed until later life when a retinitis may occur (Desmonts & Couvreur 1974). Toxoplasma only induces congenital defects after maternal primary infection in pregnancy. Infection before conception does not cause congenital disease (Desmonts & Couvreur 1987). Identification of all toxoplasma infections in the 600 000 pregnancies occurring each year in the UK would require large-scale laboratory testing (Joynson & Payne 1988), because the infection is usually asymptomatic. Screening in the first trimester would be for toxoplasma-specific IgG antibody (indicative of past infection) and for specific IgG antibody (perhaps indicative of recent infection—see below). Women never infected with *T. gondii* (390–560 000 per annum if the 1969 seroprevalence figures are correct) would require repeated IgM-specific tests throughout pregnancy (ideally at 3-week intervals (Manson-Bahr & Bell 1987). Because of the low frequency of *T. gondii* infection the IgM screening test would have to be of very high specificity. Unfortunately all toxoplasma IgM tests generate occasional false positive results (Joynson *et al.* 1989), and they cannot always be used to determine the time of onset of infection because antibody persistence is variable (4–6 or more months) (Fleck & Kwantes 1980; Payne *et al.* 1987). Thus, screening for specific IgM antibody would lead to much unnecessary concern because of false positive results or because of true positive results reflecting infection outside pregnancy when the risk to the fetus is zero (Desmontes & Couvreur 1974). Definition of the date of infection requires a battery of serological tests whose interpretation is a sophisticated process (Fleck & Kwantes 1980) and usually requires the examination of a further blood sample.

Most laboratories currently offering diagnostic services for toxoplasmosis utilize a latex agglutination technique. The latex agglutination test is a sensitive indicator of recent infection but generates a false positive rate of at least 1.3% (Holliman *et al* 1989). Positive results are therefore referred for confirmatory testing to the Toxoplasma reference laboratories (Swansea, Leeds, Tooting (London), Inverness, and Royal Victoria Hospital, Belfast) where a combination of specific IgM antibody and toxoplasma dye test assays ensure specificity. This system generates delay which creates problems if intervention in pregnancy is to be considered. Local confirmatory testing will therefore be required if mass screening for toxoplasma is introduced in pregnancy. Due to the biosafety requirements relating to the handling of the live organism (Fleck & Kwantes 1980) the toxoplasma dye test is only appropriate to reference laboratories. Toxoplasma IgM tests are potentially acceptable although a recent assessment of five commercial assays (Joynson *et al.* 1989) suggests that considerable improvement in specificity and sensitivity will be required if these assays are to serve as confirmatory tests. Those experienced in diagnosis of rubella in pregnancy are well versed in the requirements of rigorous quality control and proficiency testing which the application of such assays engender (PHLS Working Party 1988).

Even if *T. gondii* infection can be diagnosed by serological screening in pregnancy, prevention of any consequential fetal damage is likely to prove difficult. When recent infection is detected in early pregnancy, termination of pregnancy is of uncertain value. Maternal infection in the first trimester of pregnancy carries a low risk of transmission to the fetus (4–25%) but a high risk of severe damage evidenced at birth (40%) if transmission occurs (Desmonts & Couvreur 1974, 1979; Daffos *et al.* 1988) If abortion were carried out solely on the basis of maternal infection large numbers of pregnancies (at least 90 out of every 100) would be needlessly terminated.

Restriction of termination to pregnancies where fetal infection is proven (Desmontes *et al.* 1985; Daffos *et al.* 1988) would be extremely difficult. Confirmation of fetal infection requires comprehensive serological and parasitological examination of samples obtained by both cordocentesis and amniocentesis at 16 weeks. Parasitological culture is more reliable than IgM detection for the diagnosis of fetal infection (Desmonts *et al.* 1985) but results of culture may not be available for up to 6 weeks. Amniocentesis and fetal blood sampling are also procedures that may only be carried out in specialized centres and both procedures carry an inherent risk of fetal loss of up to 1%.

As an alternative to termination of pregnancy, chemotherapy given to an infected mother may prevent fetal infection. The orally administered macrolide antibiotic spiramycin has activity against toxoplasma in vitro. High blood concentrations are achieved 4–6 h after oral dosage and from 12 to 16% of the maternal blood concentrations have been detected in amniotic fluid. It is, however, uncertain whether the spiramycin concentrations following administration of 2–3 g spiramycin daily (divided doses) are adequate for treatment of the fetus *in utero*. Nevertheless, placental levels of spiramycin should suffice to treat parasitic infestation of this site. Desmonts & Couvreur (1974, 1979) reported that 3-week courses of the orally administered spiramycin alternating with 2 weeks of no treatment throughout pregnancy reduced the occurrence of congenital toxoplasmosis from 17% in historical controls to 5% (61% to 23% in third trimester infections). These studies must, however, be interpreted with caution since they did not include a concurrent control group To address this difficulty Couvreur *et al.* (1988) examined the placentas in pregnancies with recorded congenital toxoplasmosis where the mother had received either no treatment or 3 g per day spiramycin from time of diagnosis of infection Since the placenta is the key organ in maternal-fetal transmission, *T. gondii* infestation of the placenta equates with a congenital infection of the infant. Couvreur *et al.* (1988) found placental infection in a similar proportion of untreated and treated pregnancies (12/14 (86%) versus 40/45 (89%)). The efficacy of spiramycin therapy is therefore unproven.

Various clinical studies indicate the superior efficacy of a combination of pyrimethamine and sulphadiazine over spiramycin in treatment of toxoplasmosis. When Couvreur *et al.* (1988) added this combination to spiramycin therapy in the last 8 weeks of pregnancy, 50% of placentas yielded no evidence of parasite infestation. Unfortunately pyrimethamine usage in pregnancy is not recommended. Studies in animals show that pyrimethamine may cause birth defects (probably through interference in folic acid metabolism—see below) and there is a single report of antimalarial therapy (dapsone plus pyrimethamine) associated with stillbirth in a fetus with severe abdominal and thoracic wall defects and a missing left arm (Harpey *et al.* 1983). Although studies in man do not in general support the view of pyrimethamine as a teratogen, caution is warranted. Pyrimethamine inhibits dihydrofolate reductase and such inhibition may result in tetrahydrofolate deficiency (Dukes 1988). When pyrimethamine is given in the large dosage required for therapy of toxoplasmosis or when there is pre-existing folate deficiency, the inhibition of folic acid metabolism may result in megaloblastic anaemia. Folinic acid supplements must always be given concurrently and therapy in the first trimester of pregnancy is probably contra-indicated. Therapy later in pregnancy using a combination of pyrimethamine and sulphadiazine therapy is also problematic since the combination therapy is associated with significant bone marrow toxicity (leucopenia and thrombocytopenia; Hakes & Armstrong 1983) which could itself put the pregnancy at risk.

Given the lack of a vaccine to protect non-immune subjects from infection, the currently unproven prophylactic role of behaviour modification, and the lack of effective non-toxic antimicrobial chemotherapy, in our laboratory we have chosen to resist requests for toxoplasma screening of healthy pregnant women. The detection of antibody in early pregnancy will always necessitate further testing though such antibody nearly always reflects pre-conception infection. A negative result will similarly create anxiety as the patient could then be considered to be at risk of a toxoplasma infection. It is our view that toxoplasma screening in pregnancy should be restricted to patients with clinical evidence of infection (i.e., fever, lymphadenopathy or fetal abnormality *in utero*). Confirmation of recent infection following examination of a second blood specimen will then require a sober appraisal of options (vis-à-vis *in utero* diagnosis and chemotherapy). In most instances it may be appropriate to delay maternal treatment until the late stages of pregnancy, and to assess the infant at birth (including serology of cord blood and parasitological examination of the placenta) to determine if treatment is required. This strategy will not reduce the occurrence of congenital toxoplasmosis but will avoid iatrogenic wastage of healthy fetuses. Until reliable predictive indicators of severe congenital toxoplasmosis and more effective chemoprophylaxis and therapy are developed reduction of congenital toxoplasmosis will most likely result only from improved public health education concerning the routes of acquisition of *T gondii.*

Screening for human parvovirus B19 infection

Parvovirus B19 causes a relatively common childhood infection—erythema infectiosum (also known as fifth disease or 'slapped cheek syndrome') (Anderson et al. 1983). This virus also causes rubelliform and other rashes (Anderson 1987), and has been associated with aplastic crises in patients with sickle cell anaemia (Pattison *et al.* 1981) and other haematological disorders (Duncan *et al.* 1983). Arthralgia is common in patients of all ages (White *et al.* 1985).

In most studies of parvovirus B19 infections in pregnancy the fetus has not been affected (MMWR 1989). However, miscarriage in the first trimester (Mortimer *et al.* 1985), hydrops fetalis in the second trimester (Bond *et al.* 1986; Brown *et al.* 1984) and stillbirth at term (Knott *et*

Table 1. Risks of transmission and of fetal damage when a viral or protozoal infection occurs in pregnancy

	Stage of gestation			
	First trimester	Second trimester	Third trimester	Term
Rubellavirus				
Transmission	90%	70–25%*	35%	100%
Damage†	80–90%	5–17·5%††	0%	0%
Human immunodeficiency virus				
Transmission	← 24–50% →			
Damage	—AIDS develops in c 8% infected offspring per year			
Hepatitis B virus				
(1) Mother 'e' antigen positive or 'e' antigen and 'e' antibody negative				
Transmission	← Very low level →			90–100%
Damage	← Minimal →			63–90%§
(2) Mother 'e' antibody positive				
Transmission	← Very low level →			5–10%
Damage	← Minimal →			
Cytomegalovirus				
(1) Primary maternal infection				
Transmission	← 40–50% →			
Damage	← 4–5% →		?0%	?0%
(2) Recurrent maternal infection				
Transmission	← Not known, probably infrequent →			
Damage	← Not known →			
Toxoplasma gondii				
Transmission	4–25%	25–54%	65%	80%
Damage	2–10%	2–4%	0%	0%
Parvovirus B19				
Transmission	← Not known →			
Damage	← Risk of fetal death <10% →			0%

* Transmission risk reducing as pregnancy continues

† 'Damage' represents risk of significant fetal damage when mother experiences infection in pregnancy (e.g , if materno-fetal transmission occurs in 60 of 100 pregnancies and 40% congenitally infected are damaged, overall risk % = 60/100×40% = 24 damaged fetuses per 100 maternal infections).

†† Type of damage related to stage of gestation, early infection—heart and eye defects, later—hearing deficits

§ Damage = chronic virus carriage may ultimately result in hepatoma.

al. 1984) have been reported. Parvovirus B19 infection can also impair fetal erythropoiesis and so result in fetal heart failure due to anaemia (Brown 1989). The risk of fetal death following maternal parvovirus infection is uncertain but preliminary results of a prospective study of 174 affected pregnancies suggests that the risk is <10% (PHLS 1987).

Since certain animal parvoviruses are teratogenic (Siegl 1984) there has been concern that congenital malformation may follow human B19 infection. To date, there is no evidence for an increased rate of congenital malformation following infection despite the study of several hundred live born infants of B19 infected mothers (MMWR 1989). There has been one report of an aborted fetus with eye anomalies and histological evidence of multiple tissue damage (Weiland *et al.* 1987) and one report of an anencephalic fetus (Rodis *et al.* 1988) (although timing of infection in the latter case suggests that B19 virus may not have contributed to this defect (MMWR 1989)).

Screening of all pregnant women for antibody to parvovirus B19 is presently unwarranted. At least 50% of adults have antibody to the virus and are therefore immune For women infected in pregnancy there is a slightly increased risk of miscarriage or stillbirth but little risk of giving birth to a congenitally malformed child. When a pregnant women presents with a rash, B19-specific IgM antibody studies should be undertaken. The primary consideration is exclusion of rubella but identification of parvovirus B19 infection is also of importance if the risks of infection in pregnancy with this virus are to be more precisely defined (PHLS 1987).

Conclusion

When serological screening for infection in pregnancy is proposed an essential question is whether effective management is available if a positive result is obtained. Routine antenatal screening for rubella and selective antenatal screening for hepatitis B and human immunodeficiency virus infection are established procedures. The risk to the fetus of maternal infection with these agents has been documented (see Table 1) and clear guidelines for management of affected pregnancies have been defined. This is not the case for cytomegalovirus and *T. gondii* infection. The risk to the fetus following maternal infection is less precisely defined, no vaccines are available to protect non-immune women, behaviour modification has no proven role in preventing infection and no effective chemotherapy is available. *In vivo* demonstration of fetal infection is presently unreliable and is difficult to complete within an appropriate time frame. Termination of all pregnancies where infection has been proven would result in enormous fetal wastage. Further research is essential before embarking upon screening for infection with these agents in pregnancy. Development of a human CMV vaccine should form a high priority. For toxoplasma the situation is less clear, though if cats should prove to be the major source of human toxoplasmosis then development of an animal *T. gondii* vaccine may be the most efficient means of preventing human infection. The importance of diagnosing parvovirus B19 infection in pregnancy is probably minimal though further research is required.

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A morphological and immunological study of human placental bed biopsies in miscarriage

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Summary. Placental bed biopsies were examined in three groups of pregnant women for maternal vascular response to placentation as well as for the presence of cells associated with local immunosuppression activity. In the group of women undergoing legal abortion, the histological appearance of trophoblastic invasion was normal in all but one, and the proportion of immunosuppressor cells was also normal. In the missed miscarriage group the histological appearances were abnormal except in one patient. In women with a history of recurrent miscarriage who had miscarried after immunization, placentation was normal in some and defective in others. Immunosuppressor cells appeared to be diminished in number, although there was no correlation between the cytotoxic status of their sera and their pregnancy outcome.

A large proportion of recurrent miscarriages remain unexplained but recent observations in normal and abnormal pregnancies suggest the possibility of an immunological factor (Beer, 1983; Redman 1983; Mowbray & Underwood 1985). Women who fail to make a humoral immunological response to the placental antigens of the fetus tend to miscarry. This has led to the introduction of immunotherapy to improve pregnancy outcome in this group of women using either the partner's leucocytes (Beer *et al.* 1981; Mowbray *et al.* 1985) or cells from third party donors (Taylor *et al.* 1985; Unander & Lindholm 1986; McIntyre *et al.* 1986; Cauchi *et al.* 1987) or trophoblast plasma membrane infusion (Johnson *et al.* 1988). The mechanism(s) that prevent miscarriage are incompletely understood. Defective maternal vascular response to placentation has been identified in women with sporadic or recurrent miscarriage (Khong *et al.* 1987). Failure of trophoblast cells to invade the spiral arteries and to convert them to low resistance vessels could lead to fetal ischaemia and possibly death. We present further data to support these findings in women with miscarriage and extend the work to include those women who miscarried after immunotherpy. We also report on the lymphocytotoxic antibody status of the women as well as the presence of granulated lymphocytes that have been associated with suppressor cell activity in the decidua.

Subjects and methods

Three groups of women were studied, Group A included 12 women (mean age 26·5 years) who presented for termination of pregnancy; group B included 10 pregnant women (mean age 33·1 years) with a history of recurrent miscarriage (that is three or more unexplained miscarriages

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with the same partner and not more than one live birth) whose pregnancies ended in missed miscarriage even though they had been immunized with their partners blood mononuclear cells (Mowbray *et al.* 1985), and group C included six women (mean age 29·7 years), who had a missed miscarriage diagnosed by ultrasound Serum antipaternal lymphocytotoxic (APC) antibodies were tested where possible using a complement-dependent cytotoxic assay (Mowbray *et al.* 1985).

The women in group A were scanned in theatre before termination and the gestational age was determined from the fetal crown-rump length or biparietal diameter. The presence of fetal heart activity was confirmed and the placental site was located

All the women in group B were investigated in the Recurrent Miscarriage Clinic at the Samaritan Hospital for Women, London. All of them had been found to lack APC antibodies and had been immunized with their partner's white cells. Blood was collected 4 weeks after immunization and was tested for the presence of APC antibodies. The women became pregnant within a year of treatment and all of them were followed by weekly ultrasound examination as soon as their sera showed positive levels of β-human chorionic gonadotrophin. However, all the women were shown to have an anembryonic pregnancy and the placental site was determined by ultrasound.

The women in group C had had a threatened miscarriage and were assessed by ultrasound. The presence of a gestational sac but absence of fetal pole and fetal heart activity on two occasions was considered diagnostic of 'anembryonic pregnancy'.

Consent was sought from all the women for evacuation of the uterus and for obtaining biopsies from the region of the placental bed under ultrasound guidance, as described previously (Michel *et al.* 1989). Briefly, under general anaesthesia, the cervix was dilated using Hegar dilators and cervical biopsy forceps were introduced under ultrasound guidance through the cervical canal to the placental site. Biopsies were taken from under the thickest part of the placenta. There were no complications from the procedure.

Material obtained was fixed in Bouin's solution for histological study. The fixed samples were embedded in paraffin wax, sectioned at 4 µm and stained with haematoxylin and eosin (HE) and also with phloxine-tartrazine to demonstrate intracellular granules (Drury & Willington 1967). The histology was assessed by one of the authors (T.Y.K.) without knowledge of the clinical history and pregnancy outcome. The placental bed biopsy tissue was examined for utero-placental vasculature and those which did not contain enough vessels to interpret were excluded from the study. The placental bed biopsy was classified as either normal, when physiological vascular changes due to invasion by trophoblast were present, or as abnormal when these changes were absent, taking into consideration the gestational age. The physiological vascular changes were characterized by a loss of the normal musculo-elastic tissue from the wall of the arteries and deposition of fibrinoid material in which endovascular trophoblast cells were embedded. The presence of granulated cells was scored by two different observers (M.M. and D.A.C.), who had no knowledge of the clinical details. Two types of cells were observed, large granulated lymphocytes (no granules > 1 µm) and cells with large granules (at least one granule > 1 µm) as described elsewhere (Michel *et al.* 1989). The proportion of cells with large granules was calculated in each slide in relation to the total number of granulated cells. Suppressor activity in 48-h supernatants from biopsy tissues was determined as described elsewhere (Michel *et al* 1989). Trophoblastic tissue from the two miscarriage groups was sent for chromosomal analysis; 18 samples were cultured and 13 grew.

Results

The clinical details of the 28 women are listed in Table 1. In group A the placental bed showed normal development of the utero-placental vasculature with physiological changes in the decidual segments of all spiral arteries in all except one woman. However, in group C the utero-placental vasculature was inadequately developed in that most spiral arteries in the placental bed showed preservation of musculo-eslastic tissue with no evidence of involvement with migratory extravillous trophoblast in the decidual segments In group B a mixture of results was found. Four women had completely normal placental bed histology, and two others had predominantly normal utero-placental vasculature with one area of abnormal vessels. The remaining four women in this group had a poorly developed utero-placental vasculature. APC antibodies were assayed in all women in group B 4 weeks

Table 1. Histological, immunological and clinical details in the three study groups

Parity	Gestation (weeks)	APCA	Karyotype	CLG (%)	Histology
Group A: Legal abortion					
0+0	12	nt	46XX	65	normal
2+1	10	+	46XY	51	normal
2+0	8	nt	nt	75	normal
0+0	10	+	nt	60	normal
0+0	12	nt	nt	58	normal
3+2	8	nt	nt	84	normal
0+1	14	nt	nt	91	abnormal
1+1	14	nt	nt	87	normal
1+0	10	nt	nt	63	normal
0+0	9	nt	nt	62	normal
0+1	8	nt	nt	69	normal
0+0	9	nt	nt	87	normal
Group B: Treated recurrent miscarriers					
0+3	10	−	FTG	45	normal
0+9	9	+	46XX	42	? normal
0+4	10	+	46XY	21	normal
0+3	9	−	46XY	30	? normal
0+3	9	+	47XX+22	47	normal
0+5	8	−	FTG	32	abnormal
0+10	8	+	46XY	38	normal
0+5	8	+	47XY−20	31	abnormal
0+3	9	+	46XX	41	abnormal
0+3	10	−	FTG	29	abnormal
Group C: Missed miscarriage					
0+2	10	nt	46XX	34	abnormal
0+6	14	+	46XX	29	abnormal
0+4	11	−	46XX	33	abnormal
0+1	11	nt	FTG	45	normal
3+0	10	nt	FTG	71	abnormal
4+1	14	nt	46XY	38	abnormal

Abbreviations APCA = antipaternal cytotoxic antibodies; CLG = cells with large granules; FTG = failed to grow; nt = not tested; ? normal = predominantly normal with one area of 'abnormal vessels'.

after immunization and six women had seroconverted (60%), which is similar to our previous results (Mowbray 1988). APC antibodies were assayed only in two women in group A, as it was difficult to trace the partners to take blood tests, and both women had a positive test at the time of abortion Two women in group C had a history of recurrent miscarriage, one was found to have APC antibodies present in her serum, whereas the other lacked the antibodies but she was more than 40 days gestation which is our current limit for treating women in pregnancy (Mowbray *et al.* 1987). In group B, four women who developed the APC antibodies after immunotherapy had normal placental bed morphology but yet miscarried.

The percentage of cells with large granules is shown in Table 1 and related to the placental bed morphology in Fig. 1.

It is interesting the percentage of cells with large granules is significantly higher in the group having legal terminations than in the miscarriage groups ($P<0{\cdot}001$). A high proportion of cells with large granules has been associated with release of immunosuppressor factor. Interestingly, in four supernatants from samples with abnormal placental bed morphology, median suppressor activity was reduced to 63·3% compared with 87·2% in supernatants from three samples with normal placental bed biopsies, but the difference was not statistically significant because of the small numbers. It was interesting to note that there was no statistically significant correlation between the presence or absence of

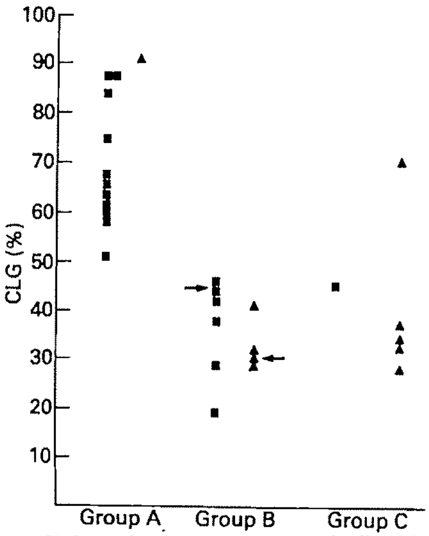

Fig. 1. Relation between percentage of cells with large granules (CLG) and histology of placental bed biopsy (■, normal, ▲, abnormal) in three groups of women. Group A = legal abortion; group B = recurrent miscarriage with immunotherapy; group C = missed miscarriage. Arrows identify a chromosomally abnormal conceptus.

the APC antibodies and the percentage of cells with large granules or with the placental bed histology.

Discussion

As expected, normal placental vasculature was found in all but one of the women having a legal abortion. The one exception does not invalidate the overall findings in this group as the background rate of miscarriage, disregarding maternal age, in apparently normal pregnancies after the first trimester is 3% (Wilson *et al.* 1986). It is also possible that the pregnancy might have progressed into one complicated by pre-eclampsia or intrauterine growth retardation, two conditions associated with defective placentation (Khong *et al.* 1986). Five of the six women with a missed miscarriage showed abnormal utero-placental arterial response to placentation. Possible explanations for the exception have been reported previously (Khong *et al.* 1987) and include failure of invasion by trophoblast to progress to transformation of myometrial segments of spiral arteries had the pregnancy progressed further, and sampling errors.

Of particular interest are the results in the women with recurrent miscarriage who had been immunized. Factors other than defective placental vasculature appear to be associated with miscarriage in some women. In mice, miscarriage with low suppression has been attributed to rejection while genetically determined fetal death has not been associated with low suppression (Clark 1988). The women with low levels of suppression (i.e., a low percentage of cells with large granules and supernatant testing) had abnormal placental bed biopsies with defective trophoblast growth and may represent 'rejection' compared with those who had higher levels of suppression and intact trophoblast growth. Further data are needed to assess this issue.

The six women in group B who produced cytotoxic antibodies to their partner's antigens had missed miscarriages, although the presence or absence of APC antibodies in maternal sera was not correlated with the percentage of cells with large granules or with normal placental morphology. This is not entirely surprising, lack of correlation of APC antibodies with pregnancy outcome has been reported by others (Regan 1988).

It is generally believed that antibodies able to block maternal T-cell recognition of paternal cells in a mixed lymphocyte reaction (MLR) are the important type of antibodies. A higher percentage of cells with large granules was associated with normal development of the utero-placental vasculature. One might speculate that immunization in these women was sufficient to allow placentation with normal trophoblastic growth to occur but not to prevent miscarriage. In this regard, it is worth noting that the percentage of cells with large granules in the immunized group with ostensibly normal placental morphology was also not in the normal range. It is of interest that one pregnancy with trisomy 22 had a high percentage of cells with large granules (97% supernatant suppression) as well as normal placental morphology but yet had a 'blighted ovum', presumably reflecting an underlying genetic cause for embryo death. It is reassuring that pregnancies with a chromosomally abnormal conceptus do miscarry spontaneously in spite of the immunization and the favourable intrauterine environment. This is consistent with the low frequency of congenital malformations among babies born to women with a history of recurrent miscarriage after immunization and this was not different from the normal obstetric population (Mowbray *et al.* 1987; Beard 1988). The generation of an immunosuppressive environment in the uterus is dependent upon both endocrine and trophoblastic signals (Daya *et al.* 1985). Granulated cell infiltration in endometrium is apparently also under hormonal control (Bulmer *et al.* 1986). How the miscarriage can be attributed to the hormonal disturbance of the underlying ovulatory disorder is not clear. It would be useful to know if women with a hormonal disturbance also had an abnormal histology and suppressor cell activity. Such data could provide further insight into the mechanism for pregnancy failure. It would also suggest a possible role for placental bed biopsies in predicting the value of various immunization regimens and the outcome of the future pregnancies.

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Embryonic heart activity: appearance and development in early human pregnancy

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Summary. The appearance and development of embryonic cardiac activity was studied in early human pregnancies established by in-vitro fertilization (IVF) using transvaginal sonography. Embryonic cardiac activity could be detected as early as 25 days after follicle aspiration. The range in appearance of embryonic cardiac activity in normal continuing pregnancies was 5 days. There was no correlation with maternal age, day of embryo transfer, or cell stage at embryo transfer. As the difference in appearance of embryonic cardiac activity was associated with a difference in crown-rump length whilst the subsequent growth curve was normal we ascribe these findings to different duration of the implantation stage. The later cardiac activity was detected the greater the risk of miscarriage. Reference curves were created relating embryonic heart rate to the number of days after follicle aspiration, the number of days that cardiac activity is present and the crown-rump length. In pregnancies ending in miscarriage heart rate patterns fell away from the reference curve. Embryonic factors seem to play an essential role in these observations.

One of the first signs of a viable pregnancy is the appearance of embryonic heart activity. Using a standard abdominal ultrasound technique, Robinson & Shaw-Dunn (1973) demonstrated this activity at 45–47 days of amenorrhoea. Ultrasound equipment has improved dramatically since then. The recent introduction of transvaginal sonography might enable detection of embryonic cardiac activity at a much earlier stage. The major advantage of this technique is that the distance between transducer and object of scanning, in this case the uterus and its contents, is greatly reduced. This creates the opportunity to use high MHz frequencies with good resolving properties. Subjects' acceptance, despite previous reservation, has been remarkably good, especially as there is no need to endure a full bladder. The in-vitro fertilization (IVF) procedure provides exact data on the time of ovulation (follicle aspiration) and the subsequent embryo transfer (ET), and therefore the duration of pregnancy This allowed us to obtain more insight into the onset of embryonic cardiac activity and its development in early human pregnancy

Subjects and methods

A total of 47 women consented to participate in the study. All women became pregnant after

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IVF treatment in our clinic. The study was approved by the ethics committee of the institution. The procedure in our centre included the transport of oocytes to the laboratory of the Department of Physiology II at the Erasmus University of Rotterdam as has been described by Jansen *et al.* (1986). The mean age of the women in the study group was 34 years (range 24–40). A pilot-study in 23 women showed that embryonic cardiac activity could not be detected before the 25th day after follicle aspiration. Based on this we designed the following protocol: transvaginal ultrasound was performed 25 days after follicle aspiration and repeated every day until embryonic heart activity appeared, then the women were scanned at intervals of 2 or 3 days until 42 days after follicle aspiration. The protocol involves between five and eight (median six) recordings of cardiac activity for each embryo. Two or 3 days were chosen at random depending on personal factors such as availability and travelling distance.

All the women were scanned between 10·00 and 12·00 h using the Diasonics DRF 400 and the Toshiba SAL 77B transvaginal probes. The former was equipped with a 5·0 and a 7·5 MHz mechanical sector scan transducer and the latter with a 5·0 MHz electronic sector scan probe. Scans were recorded by R.S. and C.A.M.J. All observations were taped and when there was heart activity the frequency was nearly always recorded by M-mode in conjunction with the real time scan (Toshiba SAL 77B) (Fig. 1). The embryonic heart rate was calculated from the M-mode or, if this was not possible, from the real time image. Embryonic cardiac activity was defined as a distinct contractile pattern inside the embryo with a frequency different from that of the maternal heart. In case of doubt both frequencies were counted simultaneously to be absolutely sure of recording the embryonic heart beat.

In 12 women the timing of onset of embryonic cardiac activity and the embryonic heart rate were determined by both R.S. and C.A.M.J. from the same M-mode recordings to exclude the possibility of inter-observer variability. Both observers also measured heart rate independently in 10 women at intervals of 15–60 min to rule out differences in heart rate over a short period of time.

The Kolmogorov-Smirnov two-sample test was used to test the distribution of embryonic heart rate and crown-rump length (CRL) of single and multiple pregnancies.

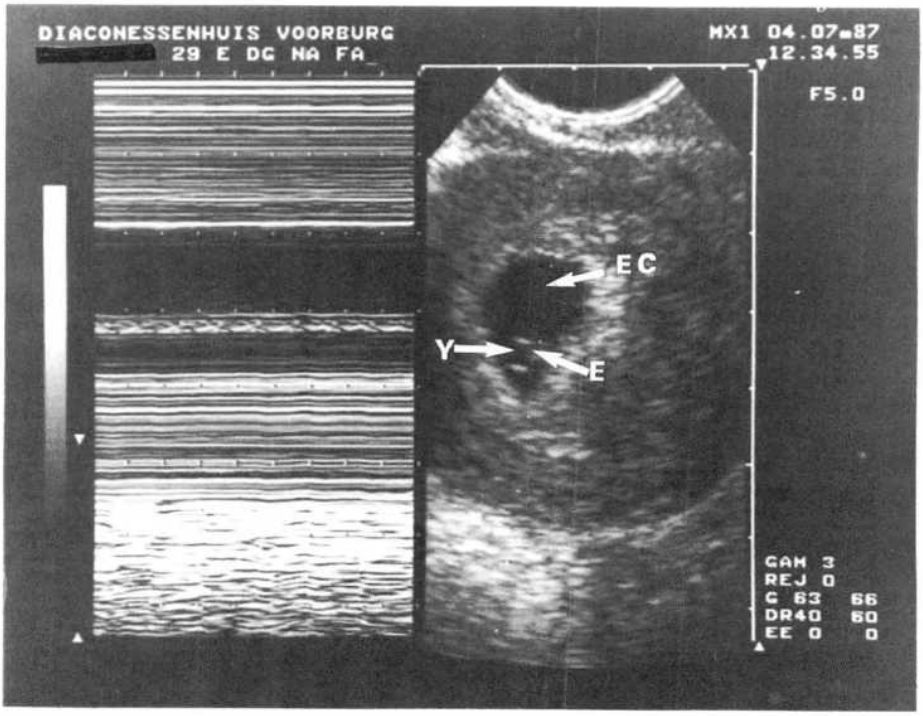

Fig. 1. Combined real time and M-mode recording of the embryonic heart rate 29 days after follicle aspiration. Y = Yolk sac; E = embryo; EC = extra embryonic coelom.

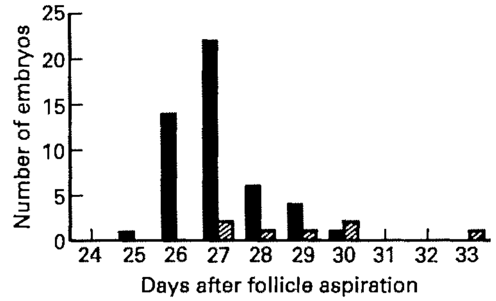

Fig. 2. The detection of embryonic cardiac activity in relation to the number of days after follicle aspiration ■ ongoing pregnancies, ▨ miscarriage in first trimester.

Embryonic heart rate was expressed as means (SD). The Wilcoxon rank sum test was used to determine the difference in timing of onset of embryonic cardiac activity between continuing pregnancies and pregnancies which later miscarried in the first trimester.

Results

There was complete agreement between the two observers for the timing of onset of embryonic cardiac activity. The inter-observer variation for embryonic heart rate determination from the same M-mode recordings was very low. The mean of the differences was 2·3 (SD 1·5, range 0–4, median 2). There was almost no variation in the embryonic heart rate over a short period of time (15–60 min). The mean of the differences was 2·9 (SD 1·7, range 0–4, median 2).

In eight out of 47 women we were not able to time the onset of embryonic cardiac activity due to personal factors such as non-availability on specific days and holidays of the women. This resulted in incomplete data from eight women (five singleton and three twin pregnancies) and complete data from 39 women (26 singletons, ten twins, three triplets) for further analysis. We included multiple pregnancies because so early in gestation development of embryonic cardiac activity and growth rate of CRL is similar in singleton and multiple pregnancies. The cumulative frequency distribution for singleton and multiple pregnancies was virtually the same suggesting they can be regarded as one population (two-tailed $P = 0{\cdot}99$). The mean of the absolute differences for embryonic heart rate (SD) and mean CRL were 2·42 (SD 1·5, range −4·4 to 5·1), 3·23 (SD 2·76, range −11·3 to 5·1), 0·37 (SD 0·27, range −1 to 0·6) and 0·29 (SD 0·28, range −0·7 to 0·6) respectively.

Figure 2 shows the distribution in the appearance of embryonic cardiac activity over the days after follicle aspiration A difference of up to 5 days was seen in the continuing pregnancies. A continuing pregnancy was defined as a gestation with a well-developed fetus identified by ultrasound 11 weeks after follicle aspiration. The time difference in appearance of embryonic cardiac activity between the group of continuing pregnancies (33 women, 48 embryos) and pregnancies that miscarried in the first trimester (six women, seven embryos) was statistically significant ($P = 0{\cdot}0028$). Figure 3 depicts embryonic

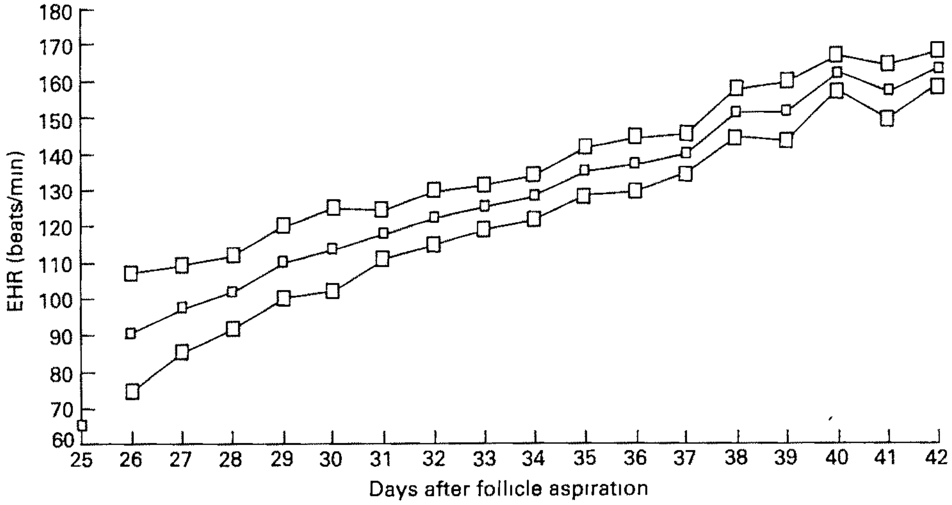

Fig. 3. Embryonic heart rate (EHR) (mean ± SD) in relation to the number of days after follicle aspiration.

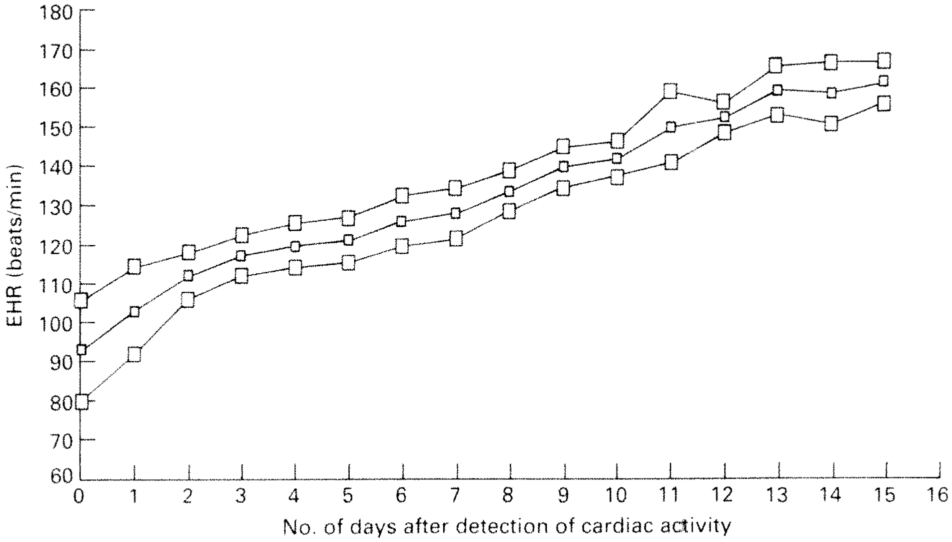

Fig. 4. Embryonic heart rate (EHR) (mean ± SD) in relation to the number of days after first detection of cardiac activity.

heart rate relative to the number of days after follicle aspiration. The number of observations per day ranged between 10 and 31 (median 17). Mean embryonic heart rate rose from 90·5 (SD 16·5) beats/min on day 26 to 163·3 (SD 4·3) beats/min on day 42 after follicle aspiration. Figure 4 shows the embryonic heart rate relative to the number of days after the first detection of embryonic cardiac activity. The number of observations per day varied between 10 and 48 (median 24). Mean embryonic heart rate gradually increased from 92·5 (SD 12·9) beats/min on day zero to 161·0 (SD 5·3) beats/min on day 15. The developmental pattern of embryonic heart rate in the six pregnancies which miscarried (seven embryos) was always abnormal when compared with the continuing pregnancies (Fig. 5). In three pregnancies abnormal heart rates preceded intrauterine death by a number of days or even weeks (range 1–17 days). In Fig. 6, embryonic heart rate is related to the ultrasonically determined CRL. The number of observations per day ranged between 11 and 35 (median 26). Mean heart rate increased from

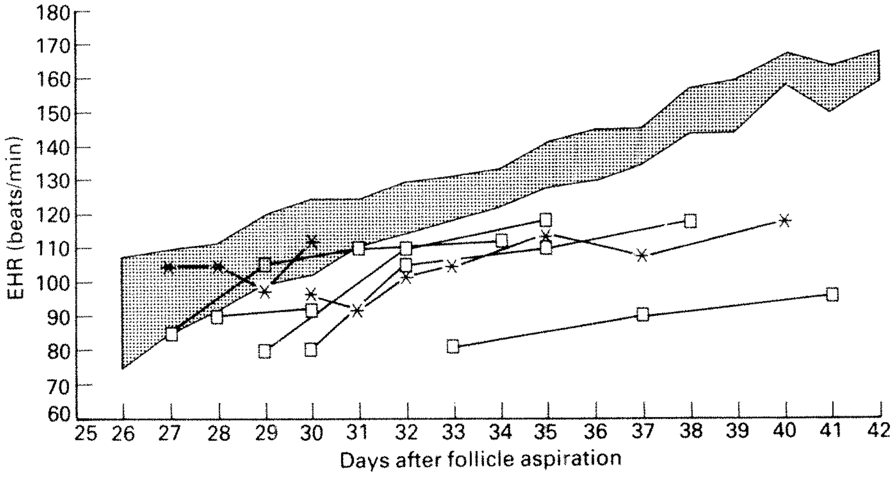

Fig. 5. Embryonic heart rate (EHR) patterns in six pregnancies (seven embryos) that ended in first trimester miscarriage. —□— singleton pregnancies, —∗— twin pregnancy. The shaded area is the reference curve derived from Figure 3.

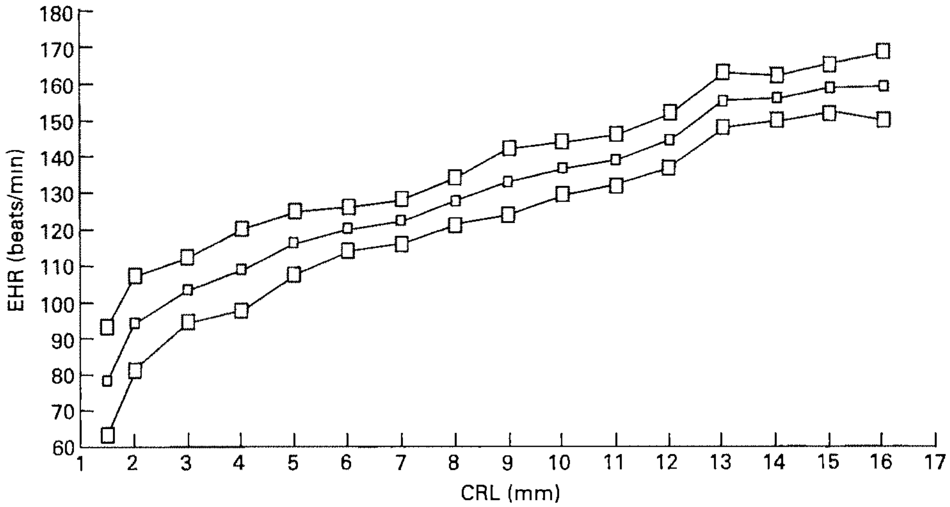

Fig. 6. Embryonic heart rate (mean ± SD) relative to the crown-rump length (CRL) in mm.

93·8 (SD 12·9) beats/min at a CRL of 2 mm to 159·0 (SD 6·7) beats/min at a CRL at 15 mm. The distribution of the heart rate determinations as well as the CRL measurements was normal.

In the present study embryo transfer was performed either 2 days ($n = 22$) or 3 days ($n = 17$) after follicle aspiration. There was no difference in timing of the first cardiac activity between these two groups (mean 27·3, SD 1·6 days compared with mean 27·0, SD 1·2 after follicle aspiration). However, six of the seven embryos that were miscarried were transferred 2 days after follicle aspiration. Excluding the miscarriages, the corrected values are 26·7 (SD 0·7) and 27·0 (SD 1·3) days after follicle aspiration; the difference is not statistically significant.

No correlation was found between the cell stage at embryo transfer (two to eight cell stage) and appearance of first embryonic cardiac activity ($r = -0{\cdot}16$).

Finally, there was a very weak correlation between the timing of first embryonic cardiac activity and maternal age ($r = 0{\cdot}18$).

Discussion

The more sensitive technique of transvaginal sonography has opened up a new field of research and provides the opportunity to study the very early stages in the development of human pregnancy.

The advantage of studying IVF pregnancies is that some of the variables such as time of ovulation (= follicle aspiration) and embryo transfer are exactly known. Whether the results can be extrapolated to spontaneous pregnancies is uncertain.

Most women in our study were older than average for pregnant women in the Netherlands, reflecting the population currently having IVF treatment.

Embryonic cardiac activity could be detected as early as 25 days after follicle aspiration. The spread of 5 days in the detection of heart activity in continuing pregnancies is considerable. Five days represents between 16·7% and 20% of the duration of pregnancy at that time. There is no clear explanation. Maternal age, the time between follicle aspiration and embryo transfer and the cell stage at embryo transfer do not seem to play a significant role. Although the timing of embryo transfer after follicle aspiration does not influence the appearance of embryonic cardiac activity, in five of the six (one twin) pregnancies that miscarried the six embryos were transferred 2 days after follicle aspiration. This observation accords with the findings by van Os *et al.* (1989), who reported a statistically significant difference in the proportion of continuing pregnancies between embryos transferred 2 days and 3 days after follicle aspiration. Other factors, most likely embryonic, in conjunction with endometrial conditions at the site of implantation might play an important role in establishing a pregnancy. Moreover, in multiple pregnancies we often observed a variation in appearance of cardiac activity between embryos, which emphasizes the importance of embryonic factors, rather than maternal variables which under these circumstances are constant (Schats *et al.*

1988). The growth potential of the embryo itself seems to be very important in the struggle for implantation. It is possible that fast dividing embryos stand a better chance of implantation, and we examined whether this division potential was related to the day of first detection of cardiac activity (Edwards *et al.* 1981) but we found no relation between cell stage at embryo transfer and the day at which cardiac activity was detected Strong, normal embryos will implant fast, but it seems impossible to judge the quality of the embryos on morphological and cleavage characteristics alone (Acosta *et al.* 1988, Edwards *et al.* 1981, Lopata *et al.* 1982). If the asynchrony in appearance of cardiac activity in multiple pregnancies indeed reflects variability in embryonic rather than maternal factors, then it is easier to understand why a later appearance of embryonic cardiac activity is associated with a higher chance of miscarriage.

Transvaginal sonography did not only enable us to detect the embryonic heart beat one week earlier than reported previously, but we also found a certain pattern in the development of the embryonic heart rate, this was about 90 beats/min on day 26 and gradually increased to about 165 beats/min on day 42. Further improvement in ultrasound equipment may elucidate the rate at which the heart tube really starts functioning. Embryonic heart rhythm appeared to be very regular, however, quantification of the beat to beat variation from M-mode recordings was not feasible. The subsequent increase in rate may be an expression of the maturation of the nervous system or an adaptation to the size of the embryo or both. This may explain the observed relation between crown-rump length and heart rate at this stage of pregnancy. The pregnancies ending in miscarriage all showed an abnormal heart rate pattern in relation to our reference curve. This deviating pattern seems to be a reflection of the reduced growth capacity of the embryo. Heart rate may start off normal, but after a few days it falls away from the reference curve.

We conclude that in continuing IVF pregnancies the date of onset of embryonic cardiac activity may differ by as much as 5 days. The later the onset of cardiac activity the greater the chance of miscarriage. The embryonic heart rate preceding miscarriage may initially be normal or lower, but ultimately falls away from the reference curve. Environmental factors do not seem to play a significant role in these findings, so we believe the factors determining onset of cardiac activity and subsequent increase in embryonic heart rate are mainly embryonic in origin.

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Large loop excision of the transformation zone (LLETZ) compared to carbon dioxide laser in the treatment of CIN: a superior mode of treatment

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Summary. A series of 199 patients with histologically confirmed cervical intraepithelial neoplasia (CIN) grade II or III were allocated by hospital number to receive out-patient treatment by carbon dioxide laser vaporization or large loop excision of the transformation zone (LLETZ). All patients received local anaesthesia. The women in the LLETZ group experienced less post operative haemorrhage, less discomfort, operative time was greatly reduced, and histological material was available for confirmation of the diagnosis. There was no significant difference in recurrence of CIN after treatment between the two groups. At 6 month follow-up, recurrence rates of 8·2% (CIN II) and 7·5% (CIN III) were observed in the laser-group and 5% (CIN II) and 5·3% (CIN III) in the LLETZ group. Further advantages of LLETZ are reduced capital expenditure and no hazard to the eyesight of the surgeon, but laser treatment is preferable in patients with widespread vaginal involvement.

Carbon dioxide laser vaporization of the transformation zone (TZ) is the most widely practised method of treating cervical intraepithelial neoplasia (CIN). The major disadvantage of this technique is that there is no histological specimen after surgery to confirm the original colposcopic and punch biopsy diagnosis. Moreover, the completeness of destruction of the lesion cannot be assessed (Partington *et al.* 1989).

Some authorities now prefer to perform cone biopsy whenever there is significant CIN, regardless of whether or not the upper margin of the TZ is visible (Partington *et al.* 1989, Baggish 1986)

Large loop excision of the transformation zone (LLETZ) is a technique being ever more widely used in the UK and Europe, but has yet to gain acceptance in the USA. The technique involves the use of fine wire loops energized with high frequency current (600 kHz) to resect cervical tissue under direct colposcopic vision.

The aims of this study were to compare laser vaporization with LLETZ in terms of the importance of obtaining a post operative histological specimen, 'cure rate', patient acceptance, peroperative and post operative haemorrhage, and operation time.

Subjects and methods

Patients were recruited from our routine colposcopy clinic, and all had been assessed colposcopically by the same surgeon All gave informed consent. Ethics committee approval

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was considered unnecessary because both treatments are routinely used in this hospital. Patients were told which method they were assigned to.

Admission criteria were: (i) colposcopically directed punch biopsy had shown CIN II or III on histological examination; (ii) there had been no previous cervical surgery; and (iii) the upper margin of the TZ was colposcopically visible.

The patients were allocated to the LLETZ or laser group by hospital number, even numbers were placed in one group and the odd numbers were placed in the other group. The study involved 199 patients.

Patients were excluded from the trial if there was a suspicion of invasive or glandular disease, colposcopically or cytologically. One woman with vaginal dysplasia was also excluded, she was treated wtih the laser.

A paracervical block and infiltration were performed using 6·6 ml of 2% lignocaine with 1:80 000 adrenaline using a dental syringe (3 ampoules of 2·2 ml each ampoule). The patient rested for 15 min to allow the local anaesthetic to act and then was placed in the lithotomy position and the cervix exposed to dilineate the TZ. A 'Force 2' electrosurgical unit (Valleylab, Boulder Colorado, USA) was used in the monopolar mode with a blended cutting and coagulation outputs of 40 and 35 W, respectively. The return electrode pad was attached to the left anterior mid-thigh. A square 10 mm cutting loop was used to resect the TZ, allowing a 2–3 mm margin on all sides. Under direct colposcopic vision, the square loop (0·006 inch gauge wire, Rocket of London Limited, Watford) was applied to the cervical surface at an angle of 90° and energized. It was then allowed to 'sink' into the cervical tissue until the crossbar was met by the surface of the cervix so that a depth of exactly 10 mm achieved. The loop was then slowly drawn downward, and the process repeated until the whole TZ was excized Between three and six 'bites' were needed to effect uniform excision to 10 mm. At the end of the procedure, the 'raw' surface of the cervix was then further coagulated using the blunt ended coagulating attachment to achieve complete haemostasis. An identical local anaesthetic was administered to patients undergoing laser vaporization. A coherent model 451 STD (California, USA) laser was used at 35 W power via the colposcope. The TZ was destroyed to a depth of 10 mm, using a 3 mm spot. Final haemostasis was achieved by defocusing the spot to 5 mm.

Patients were asked to grade the discomfort they had experienced as none, mild, moderate or severe. Peroperative blood loss was recorded by the surgeon in the same way. Patients were followed up at 3 and 6 months after treatment by colposcopy, smear and biospy if indicated.

Results

There were no significant differences between the two treatment groups with respect to age, parity, or histological diagnosis (Table 1). Good quality histological material was obtained from all 98 patients in the LLETZ group with minimal destruction of tissue at the excision margins (0·5–1·0 mm). In 91 patients, the histology confirmed the original diagnosis, but in six (6%) the post operative specimen was reported as CIN III although the original colposcopically directed punch biopsy showed CIN II. One patient originally diagnosed colposcopically and histologically as CIN III was shown to have invasive squamous cell carcinoma.

Operative time for the laser group was 4–15 min (mean 6·5 min), compared with 20–50 s (mean 16 s) for the LLETZ group. This significantly affected patient discomfort. Patients in the laser group did not experience more pain at any given time, but because of the longer operative time the laser technique was less acceptable (Table 2).

Peroperative blood loss was graded by the surgeon in the laser group as mild (9%), moderate (8%) and severe (6%), although 77% did not bleed at the time of surgery. Following laser therapy, four patients (4%) required immediate admission because of excessive bleeding, and three were later admitted with a diagnosis of secondary haemorrhage. None of the patients in the LLETZ group required admission for haemorrhage. The difference between the two groups was statistically significant ($P = 0{\cdot}008$ Fisher's exact test).

The recurrence rates at 6 months were compared between the two treatment groups, after adjusting for CIN grade, by log linear modelling using the statistical package GUM. There was no significant difference in recurrence rate between the two treatment groups ($\chi^2 = 0{\cdot}65$, $P = 0{\cdot}42$). After adjustment of the CIN grade the relative risk of recurrence after LLETZ treatment compared with laser was 0·59 (95% CI 0·13 to 2·58) (Table 3).

Discussion

Electrosurgical diathermy technology has been

Table 1. Characteristics of the women admitted to the study

	LLETZ ($n = 98$)	Laser ($n = 101$)
Age (years) mean	31	36.5
(range)	(18–52)	(22–53)
No with CIN II*	60	61
Nulliparae	41	50
No. with CIN III*	38	40
Nulliparae	22	27

*Diagnosis on punch biopsy

available for over 40 years, and was used for the treatment of chronic cervicitis. Cartier *et al.* (1981) first described the use of LLETZ in conjunction with colposcopy. They concluded that LLETZ was superior to laser vaporization because of the availability of histological material after therapy, the shorter time, and the more accurate excision of abnormal tissue, particularly with regard to depth. Boulanger (1984) also compared LLETZ with the use of the laser, but despite results similar to those described by Cartier *et al.* (1981), he concluded that the laser was superior in respect of ease of handling, exact precision and comfort (for the operator). Prendiville *et al.* (1986) reported a qualitative comparison of cervical biopsies obtained with the LLETZ method and simple punch biopsy and concluded that the former method produced superior histological material. A later report by Prendiville *et al.* (1989) described a series of 111 patients treated with LLETZ using a semicircular loop, they stressed the importance of obtaining tissue that can be examined histologically to detect otherwise unsuspected microinvasive disease.

Many authorities have reported the advantages of treating CIN by excision compared with laser vaporization, because of the availability of tissue to confirm the diagnosis, and have advocated the routine use of conization instead of vaporization in patients with significant dysplasia (Partington *et al.* 1989, Baggish 1986). Despite expectations to the contrary, they have found that problems with haemorrhage and cervical stenosis are comparable between laser vaporization and conization. Obtaining tissue for further pathological analysis may be of crucial importance. Microinvasive or invasive disease may not be apparent colposcopically (Prendiville *et al.* 1986) and may thus be under-treated if vaporization is performed (Phipps *et al.* 1989).

It is important to use minimal diathermy power consistent with efficient cutting and coagulation so that the quality of the histological specimen is preserved. Moreover, it is vital that the loop is advanced slowly to facilitate efficient surgery and the integrity of the specimen. Prolonged handling with hooks and forceps (as in laser conization) often leads to tissue distortion.

In addition to the availability of tissue specimens after treatment the LLETZ method has other advantages.

(1) Bleeding was not a problem in our series of 98 women; none had primary or secondary haemorrhage. However, the power used and the technique of final coagulation is crucial. Excessive coagulation power causes superficial charring, poor thermal/electrical penetration and haemorrhage.

(2) Operating time is very much shortened. Most patients can be dealt with in a few seconds, and the procedure is well tolerated under local anaesthesia.

(3) Using the 10 mm square loop under direct colposcopic vision, the TZ may excized very accurately, duplicating the parallel sided destruction of the TZ obtained by laser vaporization. Wright *et al.* (1984) have pointed out the advantage of removing the TZ in a parallel sided fashion, since the technique will remove tissue at an even depth, including underlying glands, in contrast to traditional cone biopsy. A further advantage over cone biospy is that a maximum of normal cervical tissue is preserved. The disadvantage in using a square loop and multiple cuts is that orientation of the specimen is lost. If this is important, then a single, cone-type excision is to be preferred.

(4) The CO_2 laser costs about £80 000 whereas

Table 2. Acceptability of the procedure in the study groups

Grade of discomfort	LLETZ ($n = 98$)	Laser ($n = 101$)
Not unpleasant	80 (82%)	32 (32%)
Moderately unpleasant	16 (16%)	50 (50%)
Very unpleasant	2 (2%)	19 (18%)

Table 3. Colposcopically diagnosed recurrences in the study groups

Histological diagnosis	Recurrences after treatment at 3 months LLETZ	3 months Laser	6 months LLETZ	6 months Laser
CIN II	0	4/61 (6 5%)	3/60 (5 0%)	5/61 (8 2%)
CIN III	0	3/40 (7 5%)	2/38 (5.3%)	3/40 (7 5%)

the LLETZ unit (Force 2, Valleylab, Colorado USA) costs approximately £4 000. Although loops are disposable, they are relatively inexpensive.

(5) The risk to eyesight from the CO_2 laser is well known and is due principally to the possibility of corneal burns from reflected or scattered beams. With the advent of the Neodymium-YAG laser, this risk is greatly increased, because stray beams are able to pass through the lens and vitreous components of the eye so that the retina is irreversibly damaged. There is no comparable hazard with the LLETZ method.

(6) One of the greatest advantages of the LLETZ method is that patients can be assessed and treated at the first visit. If the upper margin of the TZ is visible, and there is no suggestion of glandular or invasive disease, we excise the TZ using the 10 mm square loop. If the upper margin is not visible, LLETZ cone biopsy is performed. The major advantages are that a second 'treatment' visit is unnecessary provided histological examination does not reveal more serious pathology and, in the case of cone biospy, excision is complete. The patient may be assured that treatment has probably been completed and the abnormality has been dealt with. Anxiety following punch biopsy and the probability of later definitive therapy is avoided. The economic advantages are obvious.

We are now using the laser only in the treatment of patients with widespread vaginal extension of dysplasia from the cervix, and to perform dilatation of the cervical os for stenosis after previous therapy.

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Total perinatal wastage. A clarification of priorities

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Summary. The pregnancy outcome of 16 971 women carrying 17 352 living fetuses after 16 weeks gestation was studied. As well as recording perinatal deaths, all losses before 28 weeks and up to one year after delivery were recorded to give a total perinatal wastage rate of 21·6 per 1000 fetuses alive at 16 weeks compared with a perinatal mortality rate (stillbirths plus early neonatal deaths) of 7·8 per 1000 births. All deaths were then classified according to pathological sub-groups. The concept of auditing perinatal care using perinatal mortality was then compared with that using total perinatal wastage.

Perinatal mortality is the usual outcome measure for audit of perinatal care but considering only intrauterine deaths born after 28 weeks and deaths in the first week is a rather limited view of perinatal loss. Deaths before 28 weeks and after the first week can be classified into the same pathological categories as applied to conventional perinatal deaths. This has led to the suggestion that all such deaths be included as 'total perinatally related wastage' (Whitfield *et al.* 1986).

The aim of this study was to compare and contrast conventional perinatal mortality with total perinatally related wastage in a given hospital population over 3 years. The expectations would be to achieve a more realistic assessment of pregnancy loss and to clarify where priorities for research, prevention and management should lie.

Subjects and methods

The pregnancy outcome of all women who booked for delivery at Southmead Hospital, Bristol, with a living fetus of at least 16 weeks gestation and who were delivered between 1 January 1985 and 31 December 1987 was recorded. Booking normally took place at 16 weeks but women who booked later were included.

Southmead Hospital delivers the majority of women from the Frenchay and Southmead Health District of Bristol. However, due to traditional referral patterns women also come from Gloucestershire and South Wales (Table 1).

A special care baby unit is situated at the hospital and there were a number of *in-utero* transfers made for anticipated preterm delivery and possible need for neonatal intensive care. If these women were delivered at Southmead Hospital they were included in the analysis. Neonatal transfers were not included in the study

All late abortions (including terminations for congenital abnormality), early (first week) and late (up to 4 weeks) neonatal deaths and post-neonatal deaths (up to 1 year) were recorded. Late abortions and neonatal deaths were identified from obstetric, paediatric and pathology records. Post-neonatal deaths were identified from the Avon Register of infant deaths (P. Fleming, personal communication), and from the *Office of Population, Censuses and Surveys* All such losses occurring in 1988 to women delivered in 1987 were identified. These deaths were then classified according to pathological subgroups (Wigglesworth 1980). Because this classification was derived for perinatal deaths, some amendment of the definitions to include late abortions and infant deaths was necessary. Thus, three with non-immune hydrops and two

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partial hydatidiform mole were classified as 'congenital malformation'. Spontaneous miscarriages were classified under 'asphyxia' because of the acute nature of the event, whereas missed miscarriages and late intrauterine deaths were classified as 'macerated stillbirths', as death occurred before labour. Twins, cervical incompetence, sepsis and post-amniocentesis losses were classified under 'other specific' causes. Late and post-neonatal deaths directly related to preterm delivery (e.g., broncho-pulmonary dysplasia) were classified as due to 'immaturity' whereas a term baby who died of meningitis was classified as 'other specific' cause Infants dying of sudden infant death syndrome (SIDS) were classifed under 'other specific'.

Table 1. District of residence of women delivered at Southmead Hospital, 1985–1987

	n	(%)
Bristol residents	12 305	(72·5)
Non-Bristol residents	4666	(27·5)
Total	16 971	(100)

Results

There were 16 971 women with 17 352 live fetuses of at least 16 weeks gestation whose pregnancies ended in the study period. There were 60 stillbirths and 74 early (first week) neonatal deaths, giving an uncorrected perinatal mortality of 7·8 per 1000 births (Table 2). However, there were in addition 185 deaths before 28 weeks, 10 late neonatal deaths and 46 post neonatal deaths, giving a total perinatal wastage of 21·6 per 1000 fetuses alive at 16 weeks gestation (Table 3) These deaths were then classified into Wigglesworth's pathological sub-groups (Table 4)

Of the 47 deaths before 28 weeks classified as due to congenital abnormality, 32 were legal abortions and in eight the fetus died between 16 and 28 weeks and required prostaglandin induction. The other seven miscarried spontaneously.

Table 2. Perinatal mortality, 1985–1987

Total births	17 167
Perinatal deaths	
Stillbirths	60
Early neonatal (1st week)	74
Perinatal mortality rate (per 1000 total births)	7·8

Discussion

This study showed an almost threefold increase in loss if all deaths between 16 weeks and one year were considered. This increase was due to the fact that deaths before 28 weeks constituted half of the total number of deaths. These deaths before 28 weeks showed a similar proportion of 'maceration', 'congenital abnormality' and 'asphyxia' to deaths in the conventional perinatal period. However, 'other specific' causes assumed a greater importance since there were no deaths from 'immaturity' Further addition of deaths after the first week (late neonatal and post-neonatal deaths) showed that only 12% of these deaths were due to 'congenital abnormality' and 14% due to 'immaturity'. Of the deaths occurring after the first week of life 68% were due to the sudden infant death syndrome.

One valid criticism of the study is the question of how comprehensive was the identification of deaths before 28 weeks and after 4 weeks of age. We believe that our identification of deaths before 28 weeks was complete since general practitioners referring women routinely for booking at Southmead Hospital also adopt the same hospital referral practice when it comes to unbooked 'late miscarriages' or fetal deaths before 28 weeks. Although this is a hospital-based study, 72% of births occurred to residents of Bristol Health District and their outcome was fully recorded.

Comprehensive recording of post-neonatal deaths is more difficult to assess. Deaths due to immaturity and congenital malformation are likely to be complete as all the babies are followed-up locally. However, some deaths occurring to babies of non-Avon residents may not have been recorded. One would expect a post-neonatal mortality rate of 4 per 1000 births (Balarajan 1989) and thus approximately 68 deaths in the study. We have recorded 46 post-neonatal deaths, and thus we may not have accounted for

Table 3. Total perinatal wastage, 1985–1987

Total fetuses alive at 16 weeks	17 352
Deaths	
Before 28 weeks	185
Stillbirths	60
Early neonatal	74
Late neonatal	10
Post-neonatal	46
Total perinatal wastage (per 1000 'potential births')	21·6

Table 4. Pathological causes of total perinatal wastage, 1985–1987

Mortality group	Macerated *n*	(%)	Congenital abnormality *n*	(%)	Asphyxia *n*	(%)	Immaturity *n*	(%)	Other *n*	(%)
Died before 28 weeks ($n = 185$)	53	(28·6)	47	(25·4)	32	(17·3)	—		53	(28·6)
Perinatal mortality ($n = 134$)	30	(22·4)	41	(30·6)	24	(17·8)	27	(20·2)	12	(9)
Late neonatal deaths ($n = 10$)	—		6	(60)	1	(10)	2	(20)	1	(10)
Post-neonatal deaths ($n = 46$)	—		1	(2·1)	0		6	(13)	39	(85)
Total ($n = 375$)	85	(22·1)	95	(25·3)	57	(15·3)	35	(9·3)	105	(28)

Results are numbers of fetuses or infants and percentage within each subgroup shown in parenthesis.

up to one third of post-neonatal deaths. Most post-neonatal deaths are due to sudden infant death syndrome and since this is not perinatally-related, other authors have excluded such deaths altogether (Whitfield *et al.* 1986). Although this is an important number of post-neonatal deaths, the overall effect on the total perinatal wastage is minimal.

However, even if deaths before 28 weeks and after the neonatal period are underestimated, it only makes the argument for including them stronger since the deaths in the traditional period become a smaller proportion of the total perinatal wastage.

When all deaths were considered as total perinatal wastage (Table 3), only 9% were due to 'immaturity' and this must largely be due to the success of modern neonatal intensive care since the frequency of preterm delivery has remained unchanged. However, 88% of the deaths due to 'immaturity' were in babies born alive before 28 weeks gestation, of whom 16% died after the 1st week.

'Congenital abnormality' was the most common cause of death according to both methods of analysis. Unlike other attempts at classifying total perinatal wastage (Whitfield *et al.* 1986), we included terminations for congenital abnormality. This seems logical since a major part of antenatal care involves screening for congenital malformations in order to offer abortion. Of the deaths occurring before 28 weeks classified as due to 'congenital abnormality' 68% were induced abortions. Excluding these deaths would have reduced the importance of 'congenital abnormality' as a cause of death before 28 weeks from 25 to only 9.8%.

Unexplained antepartum deaths ('macerated stillbirths') remain an important cause of death, and progress in preventing such deaths has been slow. Similarly 85% of post-neonatal deaths are due to sudden infant death syndrome which remains largely unexplained.

'Asphyxia' or acute intrauterine death accounted for about one quarter of deaths in both the perinatal period and before 28 weeks. However, it should not be presumed that these are preventable since most were either spontaneous miscarriages or due to antepartum haemorrhage.

With perinatal mortality at very low levels it seems prudent to expand obstetrict audit as described here as well as in terms of morbidity (Dennis and Chalmers 1982). We have chosen to start at 16 weeks because this is when women book into the consultant unit at this hospital Once a live fetus is confirmed the women become obstetric 'patients' and come under shared responsibility of the consultant unit. Thereafter, such women expect a live baby and it seems a logical time from which to consider all fetuses that are lost.

We have used the Wigglesworth (1980) classification for its simplicity and widespread use and because it brings out the relative importance of the major causes of total perinatal loss. Other systems incorporating more detail are in use (Baird & Thomson 1969), but since many of their subgroups are so uncommon (e.g., trauma, haemolytic disease) in this hospital we have continued with a classification by major pathological subgroups only. We thus advocate the use of total perinatal wastage to report and classify unsuccessful pregnancies and the data this requires should be readily available in most obstetric units. Recording post-neonatal deaths will be the most difficult, but most perinatally-related late deaths will occur in babies under paediatric follow-up for immaturity or congenital abnormality. With further improvement in computerization and audit, comprehensive district and regional figures for total perinatally related wastage will be possible in the future.

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Anti TSH-receptor antibodies in pregnant patients with autoimmune thyroid disorder

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Summary. The study was designed to test further the usefulness of the radioreceptor assay of thyroid stimulating hormone (TSH) binding inhibitory immunoglobulins (TBII) and the bioassay of thyroid stimulating antibodies (TSAb) or TSH stimulated cAMP response inhibitory antibodies (TBkAb) in the prediction of neonatal thyroid dysfunction. Of 63 pregnant women with a current or past history of autoimmune thyroid disorder, 11 (one with active and six with a past history of Graves' disease and four with autoimmune thyroiditis) gave birth to a baby with transient hyper or hypo-thyroidism. Only high maternal titres (which could persist after partial thyroidectomy) of anti TSH-receptor antibodies (TRAb) led to neonatal hyperthyroidism. Both types of assay were able to detect the antibodies responsible for transitory neonatal autoimmune thyroid disease. TBII values reflected TSAb titres so that there was a significant correlation between the results of both assays in women with Graves' disease and in neonatal sera. Positive TBII and TBkAb activities were present in 5 of the 28 women with autoimmune thyroiditis. Therefore, when TBII is positive, the functional characterization of the antibodies warrants the use of the bioassay.

Maternal autoimmune thyroid disorders may affect fetal and neonatal thyroid function through placental transfer of anti TSH-receptor antibodies (TRAb) (Blizzard *et al.* 1960; Burman & Baker 1985). These antibodies, mainly of the IgG class, usually elicit thyroid stimulating activity but in rare cases may inhibit thyroid stimulation. Thyroid stimulating antibodies (TSAb) are usually encountered in Graves' disease, in which they are held responsible for thyroid hyperfunction (Zakarija *et al.* 1980). Although more relevant to Hashimoto's thyroiditis and autoimmune hypothyroidism (Endo *et al.* 1978; Takasu *et al.* 1987), thyroid blocking antibodies (TBkAb) have been detected in some patients with Graves' disease (Volpe *et al.* 1984). Children born to women with high titres of TRAb are therefore at risk of developing passive thyroid autoimmune hyperthyroidism (Hoffman *et al.* 1982; Zakarija & McKenzie 1983) or

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hypothyroidism (Matsuura et al. 1980; Iseki *et al.* 1983; Takasu *et al.* 1984).

In order to devise a perinatal screening for potential fetal and neonatal autoimmune thyroid disorder in pregnancies with maternal autoimmune thyroid disorder, we have measured TRAb in two ways, as stimulating or blocking antibody with a thyroid cell culture cAMP assay system, and as TSH-binding inhibitor immunoglobulins (TBII) with a radioreceptor assay of TSH.

Subjects and methods

Patients with autoimmune thyroid disease and their offspring were tested for anti TSH-receptor antibody as part of their regular investigations Thirty-five pregnant women with Graves' disease and 28 with autoimmune thyroiditis and their offsprings were studied. Blood samples were obtained from the women during the third trimester of pregnancy and from the newborn either at birth as cord blood or during the first days of life by venepuncture.

Of the 35 women with Graves' disease (Table 1) 29 had active Graves' disease and were receiving carbimazole treatment (group 1), 5–30 mg per day, at time of blood sampling. Of these 29 patients, 25 were euthyroid and four were hyperthyroid according to free T4 estimated with commercially available kits. The other six had a past history of Graves' disease for which they had undergone partial thyroidectomy (group 2). At the time of study, four of them were clinically and biochemically euthyroid without treatment the other two were euthyroid on carbimazole therapy after relapse during pregnancy. The 28 pregnant women with autoimmune thyroiditis and their offsprings were also investigated. Maternal diagnosis was made on the basis of elevated antithyroglobulin and antimicrosomal antibody titres and/or hypothyroidism or primary myxoedema. All the patients were euthyroid at the time of blood sampling, with or without T4 replacement therapy. Of these 28 women, three gave birth to a hypothyroid child and one gave birth to two hypothyroid children in two successive pregnancies. Two of these four women had had a normal child before the onset of their thyroid disease; another had had two hypothyroid children whose disease was also recognized as transient at the time of the third infant's investigations.

Table 1. Clinical data of 35 pregnant women with Graves' disease

Maternal thyroid status	*n*	Neonatal thyroid status: Euthyroid	Neonatal thyroid status: Hyperthyroid
Active Graves' disease			
Euthyroid	25	25	0
Hyperthyroid	4	3	1
Past history of Graves' disease (thyroidectomy)			
Euthyroid	6*	0	6

*Two of them had to be treated with antithyroid drugs because of overt recurrence of hyperthyroidism during pregnancy

TSAb was assayed as described previously by Madec *et al.* (1984) using human thyroid cells in monolayer culture with some modifications. The cells (10^5 cells per well) were exposed for 2 h to 40 µl of the sera to be tested or control sera in 160 µl of modified Kasagi *et al.* (1982) medium supplemented with 20 mM Hepes, 1·0mM 3-iso-butyl-1-methylxanthine (IBMx) and 0·3% BSA, pH 7·4. After incubation, cAMP released from the cells was determined by a solid phase radioimmunoassay. All samples were assayed in triplicate wells.

Stimulation was assessed by comparison with control wells. TSAb activity was expressed as a percentage of basal values.

TBkAb was determined as described previously (Madec *et al.* 1988). Sera to be tested were co-incubated with either 0·02 mU of b-TSH or 2 µl of an in-house-standard TSAb per well in the conditions of the stimulating assay. Sera were also tested alone. Presence of blocking antibodies was detected by comparison with control cells incubated in the presence of normal serum and either stimulator. Activity of TBkAb was expressed as percent inhibition as compared to cAMP concentrations obtained in the presence of the stimulators alone.

Antibodies with the capacity of inhibiting the binding of 125 I-labelled TSH to its receptors (TSH binding inhibitory immunoglobulins:TBII) were detected by radioreceptor assay (Smith & Hall 1981) using a commercial kit (TRAK-Behring). Results were expressed as U/l as recommended by the manufacturer.

Results

Patients with Graves' disease

Seven women gave birth to clinically and biochemically hyperthyroid children (FT3 range 26·4–50 pmol/l at day 0–2 of life; normal: 3·5–9). Their sera had a strongly positive TSAb activity of >350% of basal values (Fig. 1); TSAb was also detected in the hyperthyroid babies Six of these women were euthyroid and had a past history of Graves' disease (group 2); the seventh was hyperthyroid (group 1) despite carbimazole treatment (Table 1). Neonatal disease was characterized by spontaneous regression, delayed for between 4 and 24 weeks. Four infants received supportive therapy, carbimazole or propylthiouracil for 8 to 20 weeks; in none was a goitre detected by clinical examination.

The remaining 28 women in group 1 (25 euthyroid and three hyperthyroid) gave birth to clinically and biochemically euthyroid children (TSH range 7·8–48·0 mU/l at day 0–3 of life). TSAb was undetectable in 19 women and in the other nine TSAb was present but was <250% of basal values.

Sera from these 35 patients and from their children were tested also for TBII activity. The seven women who gave birth to hyperthyroid infants had TBII values of ≥40U/l. The only false-positive result was in a woman with a TBII value of 67 U/l and whose baby was euthyroid. Overall, these results are confirmatory of those obtained with TSAb assay. There was an overall significant correlation (n=70; r=0·95; P<0·001) between TSAb and TBII, although discrepancies were observed for individual sera of relatively low potency (Fig. 2).

Patients with autoimmune thyroiditis

TBkAb was assayed in all 28 women and detected in five of them (Table 2). In one of the five (no. 5), presence of the antibody was transient and her newborn was euthyroid, the other four women had very high titres of TBkAb. Blocking antibodies were detected in the three babies born to patients nos 1 and 2. Replacement therapy was initiated within 3 weeks of birth in these infants; the treatment was withdrawn after 4–10 months when blocking antibodies were no longer detectable. At 12–15 months of age, these three babies were spontaneously euthyroid. TBkAb could not be demonstrated in offspring of patients nos 3 and 4, these two babies were hypothyroid at birth and were immediately given replacement therapy because the transitory nature of the disease was diagnosed only later at 1 and 9 years of age, respectively. TBkAb was absent in the 23 other patients

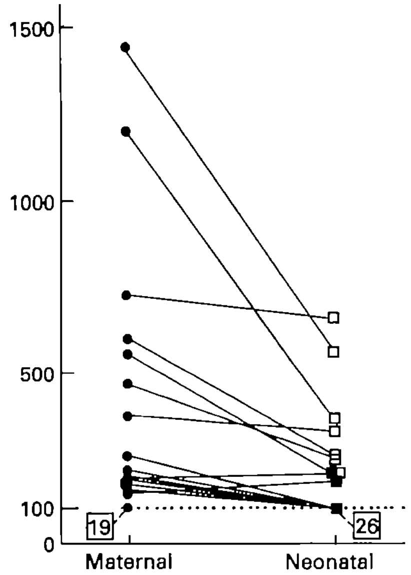

Fig. 1. Thyroid stimulating antibody (TSAb) activity in pregnant women with hyperthyroid Graves' disease and in their euthyroid (■) or hyperthyroid (□) infants. The dotted line indicates the threshold of positive titres; 19 women and 26 infants had negative TSAb values

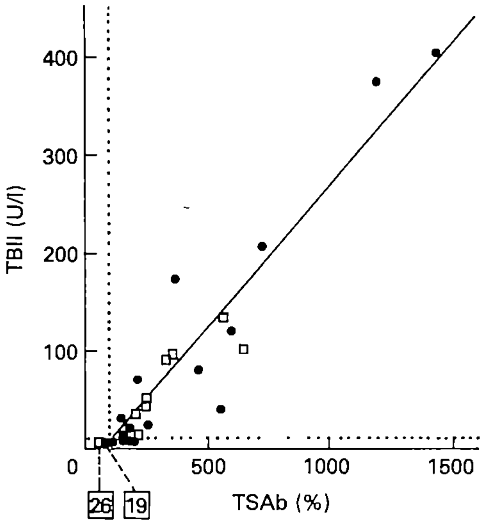

Fig. 2. Correlation between thyroid stimulating antibody (TSAb) and TS-binding inhibitor immunoglobulin (TBII) activities in maternal (●) and neonatal (□) sera in women with Graves' disease (r=0·95, P<0·0010; y=−22·29+0·29x) The dotted lines indicate the thresholds of positive titres; 19 women and 26 infants had negative TSAb and TBIII values.

Table 2. Measurement of thyroid blocking antibodies (TBkAb) in maternal and neonatal sera during six pregnancies in five women with autoimmune thyroiditis*

	TBkAb† (% inhibition)		TBII (U/l TRAK)	
Patient no.	Maternal	Neonatal	Maternal	Neonatal
1	100	100	>400	>400
2(i)	50	50	115	125
2(ii)	56	30	44	35
3	100	n.t.	>400	n.t.
4	100	n.t.	>400	n.t.
5				
In 6th month	50		20	
In 9th month	−ve	−ve	−ve	−ve

*Four women gave birth to babies with transitory hypothyroidism TBkAb was tested in 4 of the 6 newborns.

†TBkAb activity is expressed as % inhibition of the TSH stimulatory effect on thyroid adenylate cyclase activity

n.t. = not tested

−ve=negative (< 10 U/l for TBII assay).

as well as in their 23 babies. Sera from these 28 patients and from their children were assayed for TBkAb and TBII activities. No serum without TBkAb elicited TBII activity, while sera with TBkAb were TBII positive (Table 2).

Analysis of TBkAb activity

The inhibitory effect of these blocking antibodies on TSH or TSAb stimulatory activities was compared. None of the sera was cytotoxic or affected basal concentration of cAMP. Figure 3 shows the effect of increasing concentrations of the sera from patients 1 and 2. Serum from patient 1 elicited half-maximal inhibition of TSH and TSAb activities at similar concentrations approximating 0·35% (v/v of final volume). The blocking effect of serum from patient no 2 was quite different; it occurred at a much larger concentration (10%) and affected only the stimulatory action of TSH but not that of TSAb.

Discussion

In this series, prevalence of neonatal hyperthyroidism was 20% and that of hypothyroidism 18%. Obviously, the true prevalence of these conditions appears much lower and our figures are probably biased. Indeed, neonatal thyrotoxicosis is found in about 1% of babies born to women with a history of Graves' disease (Munro *et al.* 1978) while transient neonatal hypothyroidism occurs in the United States at a rate of 1 in 40 000 (Fisher 1986). However, it could be that a significant number of neonatal thyroid disorders of maternal origin are overlooked.

It is currently thought that the most useful indication of the TRAb assay is aimed at the identification of neonatal thyroid abnormalities in pregnancies complicated by these autoimmune thyroid diseases (Yagi *et al.* 1983; Matsuda *et al.* 1988; Matsuura *et al.* 1988). Since these fetal and neonatal abnormalities are dependent on autoantibodies transmitted transplacentally, this assay in maternal serum during the last trimester of pregnancy has significant prognostic value for newborn thyroid status.

Our study confirms that only high maternal titres of TSAb lead to neonatal hyperthyroidism (Dirmikis & Munro 1975; Zakarija & McKenzie 1983). These elevated titres of TSAb persisted after partial thyroidectomy in six patients. All these women were euthyroid with or without treatment. The lack of association between maternal and neonatal thyroid status is a most clinically significant point of this study. In contrast, most of the patients with active Graves' disease on antithyroid treatment gave birth to euthyroid children. Only one woman who remained hyperthyroid on antithyroid treatment

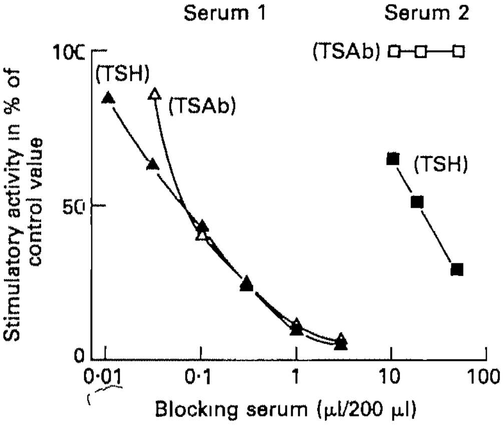

Fig. 3. Dose-effect curves of inhibitory action of two different blocking sera on thyroid stimulating hormone (TSH) (0·1 mU/ml) or TS antibody (TSAb) (1%) stimulation of cAMP production by thyroid cells. Whereas serum 1 affected TSH and TSAb stimulatory activity similarly, serum 2, at equipotent TSH inhibitory concentration, did not alter TSAb stimulatory activity.

and had a potent TSAb activity gave birth to a hyperthyroid baby. It is well known that antithyroid drugs tend to decrease the concentration of circulating TRAb (Volpe *et al.* 1986). Moreover, as they reach the fetus through the placenta, antithyroid drugs treat transferred fetal hyperthyroidism in addition to maternal hyperthyroidism, an effect that may lead to delayed onset of hyperthyroidism in the infant (Momotani *et al.* 1986). A different mechanism might explain a delay in the appearance of neonatal hyperthyroidism as reported by Zakarija *et al.* (1983) who found delayed onset of neonatal Graves' disease accounted for by the coexistence of TSAb and TBkAb in maternal serum, the latter temporarily being functionally predominant.

The presence of maternal TBII with the ability to block TSH biological activity led to transitory neonatal hypothyroidism. Similar observations have been reported previously (Matsuura *et al.* 1980; Iseki *et al.* 1983; Takasu *et al* 1984). Our patients had Hashimoto's thyroiditis and all but one were euthyroid on replacement treatment. No association between maternal and neonatal thyroid status was seen, but all the women who gave birth to hypothyroid infants had no goitre and two of them had an atrophic thyroid.

One of the aims of this study was to investigate the usefulness of the commercial kit (TRAK-Behring) in this setting in comparison with the more demanding method based on cAMP production by thyroid cells. Multiple attempts have been made to correlate TBII and TSAb activities in patients with Graves' disease. Several studies failed to find any association between these activities (Sugenoya *et al.* 1979; Macchia *et al.* 1981). In contrast, Borges *et al* (1982) and Biro *et al.* (1982) were able to demonstrate a good concordance between TBII and TSAb activities. In our patients, the correlation between the results of the two assays was largely satisfactory. Only some of the weakly positive sera in either assay appeared discordant. It is not yet clear whether discordances between TBII and TSAb are due to antibody heterogeneity or to methodological inadequacy. Of great theoretical importance is the correlation between TBII and TBkAb. Matsuura *et al.* (1988) reported a lack of concordance between these two activities, a result not confirmed by Takasu *et al.* (1987). Our five patients with TBkAb were also positive with the TRAK assay and none of the patients negative by this assay had TBkAb in their serum.

TRAb activity levels during pregnancy are useful in the prediction of neonatal thyroid dysfunction, especially in women with active, or a history of Graves' disease, or who have had a thyroidectomy for Graves' disease, or who have autoimmune thyroiditis. Neonatal transient hyper- and hypo-thyroidism should be treated with appropriate drugs, but the detection of TRAb is useful to monitor the time of drug withdrawal In those clinical situations, only high titres of TRAb are deleterious, TBII assays are suitable for the detection of both TSAb and TBkAb. Therefore, when the TBII assay is positive and regardless of clinical, historical or biological considerations, the more complex bioassay for TSAb or TBkAb is mandatory to identify the functional activity of the antibody.

In conclusion, this work illustrates the usefulness of the assay of TRAb in pregnant women with a current or a past history of autoimmune thyroid disorder. It also demonstrates the appropriateness of the readily available TBII assays. However, in selected cases, TBII assay must be reinforced by the functional bioassay. The detection of high titres of either TSAb or TBkAb in a pregnant woman is indicative of late fetal or neonatal transferred autoimmune thyroid disease.

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The effect of established and gestational diabetes on pregnancy outcome

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Abstract

Objective—To study the prevalence and type of glucose intolerance in pregnancy and the effect of different types on perinatal mortality and fetal size.
Design—A prospective case-control study with data collected by patient interview and examination of all available records during a 16-months period between 1984 and 1986.
Setting—A large maternity hospital in Kuwait where diabetes in pregnancy is common.
Subjects—The cases were a consecutive sample of 731 women, delivered during the study period, recorded in the labour ward register as being diabetic or having abnormal glucose tolerance, the control group was formed from the next woman in the register (provided she was not known to be diabetic)
Main outcome measures—Type of diabetes followed the WHO classification, with subdivision depending on level of fasting plasma glucose. Type of perinatal death was examined in detail and birthweight centile calculated.
Results—Of the 731 cases, 22% were established diabetics, most were treated with oral hypoglycaemic drugs before pregnancy and insulin during pregnancy. Of those discovered during pregnancy, 43% were classified as gestational diabetes and the remainder as impaired glucose tolerance. Overall, 50% of cases were treated with insulin. Established diabetics had a perinatal mortality rate nearly four times greater than non diabetics (RR, 3·7, 95% CI 2·6 to 6.4) and for gestational diabetics RR was 2·0 95% CI 1·2 to 3·7). Unexplained deaths were particularly common, both in established diabetics (RR, 18·4, 95% CI 3·9 to 85·7) and in gestational diabetics (RR, 13·4, 95% (CI 2·9 to 61·6). Cases with impaired glucose tolerance had no stillbirths and had a lower perinatal loss than the controls, though this was not statistically significant Heavier babies were seen in all case groups compared with controls, though the impaired glucose tolerance group had lower birthweights than the other two case groups.
Conclusions— Type 2 diabetes was found to be common, most cases being diagnosed in pregnancy. Under the conditions found in Kuwait, diabetes, in the sense of a raised fasting glucose, is accompanied by a high rate of perinatal loss from unexplained stillbirth This applies whether the condition was present before pregnancy or was discovered during pregnancy. Fetal macrosomia was also common in both situations. Impaired glucose tolerance, where fasting levels remain normal, does not appear to increase fetal loss, but may be associated with fetal macrosomia. As these women age they are likely to develop overt diabetes in the non-pregnant state, and subsequently to develop serious complications of this disease. Improving glycaemic control, both during pregnancy and subsequently, should be a priority.

Established diabetes is generally recognized as a cause of increased perinatal mortality; in one of the few total population studies, fetal death was nine times more common than in births to non diabetics (Connell *et al.* 1985). There is, however, argument about the clinical significance of abnormal glucose tolerance identified in pregnancy (Beard & Hoet 1982; Hadden 1985; Oats & Beischer 1986; Al-Sawaf *et al.* 1988). This controversy is probably due in part to true differ-

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ences in the prevalence and clinical significance of gestational diabetes in different parts of the world and to different criteria used for diagnosing abnormality. True diabetes can present in pregnancy and there is agreement that such women need to be treated. However, opinions about the management of women with lesser degrees of glucose intolerance have varied widely. Watkins (1982) suggested that women with impaired glucose tolerance should be managed in the same way as diabetic women, and Hadden (1985) considered that identification of such women may be helpful but that no specific measures were necessary, whereas Jarrett (1981) proposed that screening for diabetes in pregnancy was unnecessary

These issues are difficult to resolve in units with few cases and high standards of antenatal care, monitoring, and patient compliance. Kuwait presents an unusual but interesting situation where there are large numbers of pregnant diabetics, most of whom present only in pregnancy and, because of numbers, resources and patient compliance, monitoring and diabetic control is less close than in many centres. This has provided the opportunity to make a large prospective study of the obstetric consequences of different types of diabetes in pregnancy.

Subjects and methods

Maternity care in Kuwait is provided mainly in four government hospitals that are supposed to serve precise catchment areas, though some overlap occurs. All are staffed by consultants, with full junior staff, laboratory, anaesthetic and neonatal support. Smaller numbers of women are delivered in private hospitals or health centres. The Maternity Hospital is the largest hospital and tends to attract higher risk patients although services in the other units are now well established There is no systematic programme for screening for diabetes in pregnancy in Kuwait, but the disease is known to be common and there is a high level of awareness of the condition. Consequently, testing is performed readily when there are indications. At the Maternity Hospital data are recorded in the labour ward register, where medical complications, particularly diabetes, are reliably recorded. Each day during the study this register was inspected and a note made of each woman recorded as being 'diabetic', or having 'abnormal glucose tolerance' together with the next woman in the register (providing she was not known to be diabetic) as a control. Each case and her control were then interviewed the day after delivery and a detailed 54 item form completed. The obstetric notes and any separate antenatal files were examined, and in some cases information was obtained from polyclinic records.

Until November 1985, plasma glucose was measured using a neo-cuproine method (Technicon auto-analyser) and, as this tends to give slightly higher results than glucose oxidase, plasma glucose was corrected according to the formula: glucose (glucose oxidase method) = glucose (neo-cuproine method) $\times$ 1·11 $-$ 19·3 mg/100 ml. (Technicon Corporation Tanytown NY). From November 1985 plasma glucose was measured using a glucose oxidase/peroxidase method (Technicon auto-analyser). Where 50 g oral glucose tolerance tests were used, 2-h post-load plasma glucose was assumed to be 1 mmol/l higher to equate with 75 g glucose load (WHO 1980). Venous plasma was used throughout.

Diabetes was classified as 'established' if the disease was known to be present, and was being treated, before pregnancy. Where diagnosis was made only during pregnancy the WHO (1980) criteria were used, with the following subdivisions 'Gestational diabetes' was where fasting plasma glucose was equivalent to $>5{\cdot}8$ mmol/l on at least two occasions, corresponding to the category A_2 of Freinkel *et al.* (1985) and recognized by the Second International Workshop—Conference on Gestational Diabetes Mellitus (1985) as an indication for insulin therapy in many centres. 'Impaired glucose tolerance' was defined as a plasma glucose level of >8 mmol/l 2 h after a 75 g load, with a fasting glucose $<5{\cdot}8$ mmol/l. Some patients did not have glucose tolerance test results available, but had been classified as 'abnormal glucose tolerance' and had no evidence of raised fasting glucose. They have been included in the 'impaired glucose tolerance' group. Birthweight for gestation was calculated as standard deviations from the mean allowing for parity, gestation and sex of the child (Altman & Coles 1980).

Data were recorded on the questionnaire forms, and then transcribed to summary sheets which were later processed in Edinburgh. The data were entered into the Edinburgh University Main Frame Computer for Analysis using SPSS-XX.

Results

The study ran for 16 months from 1984 to 1986.

Table 1. Perinatal mortality

Group	All deliveries	All babies	Stillbirths (per 1000 births)	Early neonatal deaths (per 1000 livebirths)	Perinatal deaths (per 1000 births)	Unexplained intra-uterine deaths (per 1000 births)
Total hospital population	23 567	23 831	265 (11)	255 (11)	520 (22)	not known
Controls	731	739	9 (12)	10 (14)	19 (26)	2 (3)
Total cases						
Insulin	362	365	17 (47)	6 (17)	23 (64)	15 (41)
No insulin	369	371	2 (5)	2 (5)	4 (11)	2 (5)
Total	731	736	19 (26)	8 (11)	27 (37)	17 (23)
Established diabetes						
Insulin	147	147	8 (54)	5 (36)	13 (88)	8 (54)
No insulin	14	14	– (0)	– (0)	– (0)	– (0)
Total	161	161	8 (50)	5 (33)	13 (81)	8 (50)
Gestational diabetes						
Insulin	180	182	9 (49)	– (0)	9 (49)	7 (38)
No insulin	66	66	2 (30)	– (0)	2 (30)	2 (30)
Total	246	248	11 (44)	– (0)	11 (44)	9 (36)
Impaired glucose tolerance						
Insulin	35	36	– (0)	1 (28)	1 (28)	– (0)
No insulin	289	291	– (0)	2 (7)	2 (7)	– (0)
Total	324	327	– (0)	3 (9)	3 (9)	– (0)

During this time data were collected on 731 cases and controls (736 and 739 babies respectively). This represents 548 cases per annum or 3·1% of all deliveries

Of the 731 cases 161 (22%) were established diabetics, 118 of them (73%) were White class A and had been treated with oral hypoglycaemic drugs or diet before pregnancy and most received insulin during pregnancy (14 treated with diet before pregnancy continued to be treated by diet). Of the others 28 (17%) were class B, 12 (7%) were class C and three were class D

Of the 570 cases discovered during pregnancy 246 (43%) were classified as gestational diabetes and the other 324 (57%) as impaired glucose tolerance. Of the gestational diabetic group 40% were known to have fasting plasma glucose levels >8 mmol/l on at least two occasions and were thus unequivocally diabetic. Of the cases with impaired glucose tolerance 60% were known to have a 2-h glucose >9 mmol/l which is the 95th centile in the 3rd trimester (Lind, 1989) Of the cases diagnosed in pregnancy 215 (38%) were treated with insulin during pregnancy as were 157 of the 161 established diabetics (an overall proportion of 50%).

Table 1 shows that the perinatal mortality rate in the selected controls was similar to that in the total hospital population. The total perinatal death rate was significantly higher in the diabetic group than in the rest of the hospital population ($\chi^2 = 7{\cdot}2$, $P<0{\cdot}01$), because of an excess of stillbirths. This was due to the high rate of loss in both established diabetics and gestational diabetics. Expressed as relative risks (RR), the overall perinatal death rate in diabetics was 1·7 times that of non-diabetics (95% confidence interval 1·2 to 2·5). For established diabetics the relative risk was 3·7 (2·2 to 6·4) and for gestational diabetics it was 2·0 (1·2 to 3·7). Unexplained intrauterine deaths were much more common in established diabetics (RR = 18·4; 95% CI 3·9 to 85·7) and gestational diabetics (RR = 13·4, 95% CI 29 to 61·6).

The cases with impaired glucose tolerance had no stillbirths and had a lower perinatal loss than the controls, though this difference was not statistically significant ($\chi^2 = 2{\cdot}3$).

Analysis of the subgroup of diabetics who used insulin showed similar differences overall, with higher perinatal death rates among insulin users. The distribution of insulin use is, of course, closely related to the diabetic group, and the data do not allow us to identify an independent statistically significant effect of either insulin use or diabetic group after the other variable is taken into account. There is, however, a tendency for established diabetics to have the higher perinatal death rates among insulin users, and insulin users have higher perinatal death rates in all diabetic groups.

Table 2 shows that the excess loss is of macerated stillbirths with no other explanation for the deaths. These stillbirths tended to occur in late pregnancy and to be macrosomic.

Table 3 shows that babies in the control group are heavier than expected compared with centile data derived from Scottish births, with a mean birthweight standard deviation score of +0·42 and three times as many babies as expected weighing ≥2 SD. However, birthweight was highly significantly greater in cases than in controls, both in terms of birthweight >4·5 kg and birthweight centile. Interestingly, this increase in birthweight was seen also in the group with impaired glucose tolerance, though there were significant differences between case groups. There were no significant differences in any aspect of birthweight depending on whether or not there was treatment with insulin. Only 21% of the cases were ever seen by a dietician.

Discussion

It is important to emphasize the limitations, and the advantages, of the study design. This is not a total population study, and there may be some bias in referral. There is no systematic screening for glucose intolerance in pregnancy in Kuwait, and this may also introduce bias in selection. Definitions of abnormality and treatment were not standardized for clinical management and the information available in the antenatal notes was often inadequate. In many cases very few blood glucose measurements were made On the other hand, this is a very large survey in an area where gestational diabetes is common. Every patient known to be affected was included, and follow up was scrupulous. As there are several fully equipped obstetric services in Kuwait, this study will give a reasonable guide to the prevalence and type of diabetes found. Finally, there is a high rate of perinatal death and big babies, and because of this and the size of the study, very clear differences between groups have been demonstrated Even a large multicentre study in Europe (and this would have many of the same disadvantages referred to above) would be unlikely to show this so clearly. This Kuwait study is therefore of major importance as a reflection of the effect of different degrees of glucose intolerance on pregnancy outcome.

There are few published total population studies of diabetes in pregnancy, and all have disadvantages. A study based on birth registrations in Norway estimated a population rate of 3 per 1000 births (Jervell *et al.* 1980) whereas Wheeler *et al.* (1982) estimated a rate of 5·9 per 1000 births in South Carolina, USA, again using birth certificates and hospital discharge abstracts. However, neither study clearly differentiated between gestational and established diabetes, and the criteria for diagnosis are not known. A later population based study by Connell *et al.* (1985) in Washington State, USA, concluded that the prevalence of pre-existing diabetes was 2·1 per 1000 total births. Using data from the US National Natality and Fetal Mortality Survey of 1980, Sepe *et al.* (1985) reported prevalence of 'overt' (Types I and II) diabetes in pregnancy of 7·8 per 1000 births but it is not clear from their paper whether their much higher prevalence included cases diagnosed in pregnancy. These studies all share the advantages of being large, and population based, but diagnostic criteria are unknown, and there may be significant underreporting. Our figure for established diabetes (6·8 per 1000 births) is somewhat higher than most of the above studies.

However, although the prevalence of established diabetes in pregnancy in Kuwait may not be greatly increased, there are very marked differences in the distribution of type of diabetes compared with other published series, and these cannot be explained by pattern of referral. The number of women with White Class C, D, F or R diabetes, and who can be assumed to have true Type I diabetes, is low (9% of established diabetics or 0·6 per 1000 births). This is in keeping with the population study performed in Kuwait in men and non pregnant women by Taha *et al.* (1983). On the other hand the proportion of women who entered pregnancy known to be diabetic, and controlled either on diet or oral hypoglycaemic drugs, is very high (73% of cases or 5 per 1000 births) and suggests that, unlike Type I diabetes, Type II diabetes is unusually common. This may relate partly to high age and parity, but weight and genetic predisposition may be more important determinants.

This high prevalence of Type II diabetes was seen also in cases discovered in pregnancy. Overt diabetes was common, and as many of these cases were discovered in early pregnancy there are undoubtedly many women whose diabetes predated the pregnancy, but was not recognised. As well as the 99 women with overt

Table 2. Details of perinatal deaths

Group	Age (years)	Parity	Treatment during pregnancy	Gestation (weeks)	Birth-weight (g)	Type of death	Clinical
Control							
	21	3 + 1	–	33	3100	Macerated SB	Unexplained
	29	0 + 1	–	30	1300	Fresh SB	Placental abruption
	38	3 + 0	–	39	3650	Macerated SB	True knot in cord
	29	1 + 3	–	?	3100	Macerated SB	Unexplained
	24	1 + 0	–	42	3000	Macerated SB	Placental abruption
	35	3 + 0	–	32	3800	Macerated SB	Ascites, multiple congenital anomalies
	27	1 + 1	–	28	800	Fresh SB	Congenital anomaly
	23	0 + 0	–	34	2250	Fresh SB	Sickle cell crisis
	20	0 + 0	–	39	3000	Macerated SB	Severe pre-eclampsia
	28	0 + 0	–	27	1000	NND	Immaturity
	27	0 + 6	–	40	3350	NND	Multiple anomalies
	35	10 + 4	–	37	3200	NND	Asphyxia
	36	2 + 2	–	25	879	NND	Immaturity
	19	0 + 0	–	41	3250	NND	Congenital heart disease
	22	0 + 0	–	27	822	NND	Immaturity
	22	3 + 0	–	40	4300	NND	Congenital heart disease
	22	0 + 0	–	32	1814	NND	RDS, severe pre-eclampsia
	28	1 + 2	–	24	700	NND	Immaturity
	35	7 + 3	–	27	1000	NND	Immaturity
Established diabetes							
	30	4 + 0	Insulin	37	3500	Macerated SB	Unexplained
	35	7 + 0	Insulin	38	5000	Macerated SB	Unexplained
	42	8 + 2	Insulin	38	3800	Macerated SB	Unexplained
	40	4 + 0	Insulin	38	4000	Macerated SB	Unexplained
	21	0 + 1	Insulin	39	2000	Fresh SB	Unexplained
	28	6 + 0	Insulin	38	4500	Macerated SB	Unexplained
	35	14 + 0	Insulin	33	2150	Macerated SB	Unexplained
	38	9 + 0	Insulin	30	1200	Macerated SB	Unexplained
	33	1 + 0	Insulin	37	3600	NND	Diaphragmatic Hernia
	29	9 + 0	Insulin	30	1350	NND	Immaturity
	37	8 + 1	Insulin	30	1400	NND	Immaturity
	?	4 + 2	Insulin	40	3800	NND	Cardiac anomaly
	38	9 + 0	Insulin	37	3900	NND	Multiple anomalies
Gestational diabetes							
	26	1 + 0	Diet	33	1500	Macerated SB	Unexplained
	38	5 + 1	Insulin	35	3400	Macerated SB	Unexplained
	32	3 + 2	Diet	39	4300	Macerated SB	Unexplained
	36	8 + 0	Insulin	39	5000	Fresh SB	Shoulder dystocia
	32	4 + 1	Insulin	37	4000	Macerated SB	Unexplained
	38	7 + 0	Insulin	36	1700	Macerated SB	Unexplained
	24	2 + 0	Insulin	39	3250	Macerated SB	Unexplained
	32	1 + 1	Insulin	31	1300	Macerated SB	Unexplained
	30	11 + 0	Insulin	39	4400	Macerated SB	Unexplained
	31	3 + 0	Insulin	37	4000	Macerated SB	Unexplained
	34	7 + 1	Insulin	40	2700	Macerated SB	Anencephaly
Impaired glucose tolerance							
	31	3 + 2	Insulin	38	3250	NND	Not stated
	28	1 + 1	Diet	26	640	NND	Immaturity
	19	0 + 1	Diet	30	1420	NND	Immaturity

SB Stillbirth, RDS Respiratory distress syndrome, NND Neonatal death

Table 3. Birthweight in the study groups

Group	Total deliveries	Total babies*	Birthweight ≥4·5 kg n (%)	Birthweight SD score Mean (SD)	Birthweight SD score + 2 SD n (%)
Control	731	739 (703)*	13 (1·8)	+0·42 (1.10)	68 (9·7)
Total cases	731	736 (692)	68 (9·2)	+1·17 (1.20)	182 (26·3)
Established diabetics	161	161 (151)	17 (10·6)	+1·21 (1·27)	45 (29·8)
Gestational diabetics	246	248 (236)	28 (11·3)	+1·38 (1·27)	80 (33·9)
Impaired glucose tolerance	324	327 (305)	23 (7·0)	+0·99 (1·12)	57 (18·7)
Comparison of cases and controls			$\chi^2 = 38{\cdot}0$ $P<0{\cdot}0001$	$t = 12{\cdot}2$ $P<0{\cdot}0001$	$\chi^2 = 64{\cdot}4$ $P<0{\cdot}0001$
Comparison within diabetic groups			$\chi^2 = 3{\cdot}5$ NS	$f = 7{\cdot}2$ $P<0{\cdot}0001$	$\chi^2 = 17{\cdot}1$ $P<0{\cdot}0001$

* The number in parenthesis shows the number of babies for whom the birthweight standard deviation (SD) score could be determined, missing babies had either uncertain gestation, were born before 33 weeks, or sex was unknown

diabetes there were 147 who had at least two raised fasting glucose levels >5·8 mmol/l and a further 35 women were treated with insulin. Thus nearly 50% of the cases diagnosed in pregnancy can be assumed to have significant abnormality of glucose tolerance. This is inevitably an underestimate. Comparison with other studies is difficult, the great range being mainly due to different definitions used in differently selected populations, but the number of patients requiring insulin in the Kuwait study is high.

Compared with controls, the cases had only a modestly raised perinatal mortality, which was surprising in view of the poor compliance of many women with suggested dietary and insulin regimens and even with medical recommendations for monitoring or elective delivery. Nevertheless, these overall figures conceal large differences within diabetic groups and with particular types of perinatal death. Thus established diabetics had a perinatal mortality rate nearly four times greater than the non-diabetic population and the rate of unexplained intrauterine death was 18 times more common than in controls, (95% CI 3·9 to 85·7). A recent report from the state of Hesse, FRG, has shown that unexplained fetal death there is seven times more common in diabetic women than controls (Lang & Kunzel, 1989). Women with gestational diabetes had a similarly high risk of stillbirth, and in particular unexplained intrauterine death. However, the group with impaired glucose tolerance did not experience stillbirth and had a lower perinatal mortality rate than controls. It is doubtful whether this group is at increased perinatal risk (Hadden, 1980). Although Watkins (1982) recommended that pregnant women with impaired glucose tolerance (post load blood glucose >8 mmol/l) should be managed as if they had overt diabetes, such intensive care for such a large proportion of the population seems inappropriate and unrealistic. However, it should be remembered that our classification is retrospective. It does not address the question of how many women started with impaired glucose tolerance in early pregnancy and then developed overt diabetes later in pregnancy. Our statements apply only to women with impaired glucose tolerance who were never observed to have a raised fasting glucose.

Big babies were much more common in the cases than in the controls. Interestingly big babies were seen in all study groups, including the group with impaired glucose tolerance. This may partly be due to selection bias and will also be related to higher maternal weight in the cases but it is in keeping with the findings of Al-Shawaf *et al.* (1988) of the effect of borderline levels of glucose intolerance on macrosomia. There is also the effect of treatment to be considered, with reduction in birthweight in patients treated with insulin. This may explain the absence of difference in birthweight between cases treated with insulin and those treated with diet.

From the obstetric point of view the conclusions seem clear. Diabetes, in the sense of a raised fasting glucose, is accompanied by a high rate of perinatal loss from unexplained macerated stillbirth. This applies equally whether the condition predated pregnancy or was discovered during pregnancy. Fetal macrosomia is also common in both situations. Impaired glucose tolerance, where fasting glucose levels remain normal, does not appear to cause increased fetal loss, but may be associated with fetal macrosomia.

Finally, there are important long term implications from this study. As these women age they are likely to develop overt diabetes in the non-pregnant state, and subsequently develop serious complications of this disease. The opportunity to try to alter lifestyle to prevent this process is present in pregnancy, but only 21% of the diabetic group ever saw a dietician, and more detailed information with routine screening, and assessment of approach to dietary advice is urgently needed.

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Gonadotrophin releasing hormone agonist (buserelin) in the treatment of endometriosis: changes in the extent of the disease and in CA 125 serum levels after 6-month therapy

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Summary. Twenty-two women with endometriosis were treated with the luteinizing hormone-releasing hormone (LHRH) agonist buserelin for 6 months. At second-look laparoscopy the mean score of endometriosis had decreased from 23·1 (SD 17·0) to 17·2 (SD 20·2) ($P<0·05$). CA 125 serum levels decreased from 38·4 (SD 32·2) U/ml at diagnosis to 15·5 (SD 7·0) at second look ($P<0·005$). CA 125 levels correlated at diagnosis with total score of endometriosis ($P<0·05$) and with active score of endometriosis ($P<0·05$), but not with the adhesion score. CA 125 levels were not correlated with endometriosis scores at second look laparoscopy, thus suggesting that mechanisms other than the change in the extent of the disease may be involved in the CA 125 decrease during therapy. CA 125 levels may therefore not be a reliable indicator for monitoring the efficacy of LHRH agonist treatment of endometriosis.

Endometriosis is a disease of the reproductive years and may be associated with pelvic pain, dysmenorrhoea, dyspareunia and infertility. It has been observed in 1%–7% of women of reproductive age (Simpson *et al.* 1980, Strathy *et al.* 1982, Kirshon & Poindexter 1988), and in 15%–30% of women with infertility (Kistner 1979).

Recently it has been shown that long-term administration of luteinizing hormone-releasing hormone (LHRH) analogues causes a reversible desensitization of pituitary receptors for endogenous LHRH (down-regulation) resulting in a reduction of plasma oestrogen levels to approximately postmenopausal values (Meldrum *et al.* 1982, Lemay & Quesnel 1982, Schriock *et al.* 1985). This temporary and reversible pseudo-menopausal state may be useful in the treatment of endometriosis.

CA 125, a cell-surface glycoprotein identified by monoclonal antibody OC-125 (Bast *et al.* 1981), is elevated in some women with endometriosis (Barbieri *et al.* 1986; Patton *et al.* 1986; Pittaway & Fayez 1986; Fedele *et al.* 1988) If this antigen is specific for endometriosis, serum levels should decrease as endometriosis responds to LHRH agonist treatment.

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The present study is a prospective assessment of LHRH agonist treatment of endometriosis in terms of the change in the extent of the disease and in relation to the change in CA 125 levels. If CA 125 reflects the extent of the disease, it could be a noninvasive method to monitor medical treatment of endometriosis.

Subjects and methods

Since January 1987, in the department of obstetrics and gynaecology of the Catholic University in Rome, medical treatment for endometriosis has been confined to women with infertility-associated endometriosis of stages III and IV (American Fertility Society classification of endometriosis (AFS): American Fertility Society 1985) as a first step of a combined medical-surgical treatment plan, or to women with endometriosis-associated pelvic pain, dysmenorrhoea or dyspareunia severe enough to necessitate treatment, regardless of stage.

This study reports 22 women undergoing laparoscopy during the luteal phase of the cycle, found to have endometriosis requiring medical treatment according to the protocol. Seven suffered from infertility and 15 from severe endometriosis-associated pelvic pain; they all agreed to enter the protocol, and completed it. Their mean age was 29 years (range 20–41). Three patients had stage I disease, four had stage II, 12 stage III and three stage IV. Before treatment, dysmenorrhoea was present in 17 patients (77%), chronic pelvic pain in 14 (64%) and dyspareunia in 10 of the 20 sexually active women (50%). No surgical procedures were performed at the time of diagnostic laparoscopy.

Treatment consisted of buserelin (Suprefact, Hoechst Italia Sud, Scoppito, Aquila, Italy) 200 μg subcutaneously twice a day for 5 days, followed by 400 μg intranasally 3 times a day for 6 months Buserelin was started in the early follicular phase, day 2–3 of the cycle, in the first 12 patients, and in the second half of the luteal phase in the following 10 patients to prevent transient stimulation of follicular activity with the initial rise of serum oestradiol (Lemay *et al.* 1988a).

A second look laparoscopy was performed at the end of the 6-month therapy. All diagnostic and second look laparoscopies were performed by the same observer (R.M.).

Women were assessed for symptoms every month during therapy. Venous blood samples for CA 125 determination were drawn at the time of admission for the first and second look laparoscopy, and monthly at the follow-up visits in between. Plasma was separated by centrifugation and stored at −20°C. CA 125 was measured by radioimmunoassay kits (CIS diagnostici, Santhia', Vercelli, Italy). Intra-assay and inter-assay coefficients of variation were 8% and 15% respectively.

Differences between AFS scores before and after treatment with buserelin and between CA 125 levels before and after treatment were assessed using the Wilcoxon signed rank test Correlations between AFS scores and CA 125 levels before and after treatment were examined using the Spearman rank correlation coefficient.

Results

At second look laparosocpy the mean total AFS score decreased from 23·1 (SD 17·0) to 17·2 (SD 20·2) ($P<0·05$). The decrease was accounted for by the decrease in active lesions score from 17·2 (SD 11·0) to 11·3 (SD 11·7) ($P<0·005$) while the score due to adhesions remained unchanged (Table 1). For endometriosis score, there was an improvement in 15 women (68%), no change in three (14%), whilst four (18%) scored worse due to *de novo* adhesion formation in two and worsening of previous adhesions in the other two. For stage of endometriosis, six women were assigned at the end of therapy to a lower stage, while 16 remained in the same one. Endometriosis-associated symptoms disappeared in all patients within 4 months from the beginning of treatment.

Side effects were reported at some time during treatment by all patients, but they were never so severe as to preclude completion of treatment: hot flushes were reported within 1 month of treatment by 20 women (91%) Other com-

Table 1. Mean AFS scores before and after 6-month LHRH-analogue treatment of endometriosis in 22 patients

	Mean AFS score (SD) Before	After	Variation
Total score	23·1 (17·0)*	17·2 (20·2)*	−26%
Active score	17·2 (11·0)†	11·3 (11·7)†	−34%
Adhesions score	5·9 (9·0)	5·9 (12·5)	0%

Significance of difference between before and after treatment *$P<0·05$, †$P<0.005$

plaints were: vaginal dryness (82%), fatigue (77%), decreased libido (73%), headache (59%), dyspareunia due to decreased vaginal secretion (55% of the sexually active women), insomnia (45%).

Amenorrhoea was present in all patients within 3 months of the start of treatment. There was no difference in the prevalence of bleeding episodes between women who started treatment in the early follicular phase (three of 12 had up to two episodes of subsequent uterine bleeding) and women who started treatment in the luteal phase (three of 10, up to three episodes).

The plasma levels of CA 125 decreased from a mean value of 38·4 U/ml (SD 32·2) before therapy to 15·5 U/ml (SD 7·0) at the completion of therapy ($P<0{\cdot}005$) (Table 2). CA 125 levels decreased in all but one patient. Considering significant an increase or a decrease of 40% or more (which is more than twice the interassay coefficient of variation), there was a decrease in 14 patients. The disease regression correlated with a decrease of 40% or more in CA 125 levels in seven of the 22 women (32%). The total AFS score correlated with CA 125 levels at the diagnosis ($r=0{\cdot}45$, $P<0{\cdot}05$) but not after treatment ($r=0{\cdot}11$, $P>0{\cdot}05$). The score of active lesions before treatment correlated with CA 125 levels ($r=0{\cdot}47$, $P<0{\cdot}05$), whereas the adhesion score did not ($r=0{\cdot}19$, $P>0{\cdot}05$). Within the post treatment values, neither the score of active lesions correlated with CA 125 levels ($r = -0{\cdot}02$, $P>0{\cdot}05$), nor did the adhesion score ($r = -0{\cdot}17$, $P>0{\cdot}05$).

Discussion

The results reported in this study in a group of 22 women with endometriosis confirm the efficacy of buserelin in the treatment of this disease.

The decrease in endometriosis score we observed after 6 months of therapy with this LHRH analogue corresponds to that reported in the literature. However, the variation we observed for the total score is less than that reported by other authors.

Table 2. Serum CA 125 levels in 22 patients undergoing 6-month buserelin treatment

	Serum CA 125 (U/ml)	
Months of treatment	Mean (SD)	Range
Basal	38·4 (32·2)	10–140
1	19·8 (10·1)*	10– 42
3	16·1 (7·1)†	5– 28
6	15·5 (7·0)†	5– 35

Significance of difference compared with basal vlaues *$P<0{\cdot}05$, †$P<0{\cdot}005$

In terms of implant score, Steingold *et al.* (1987) reported a 78% reduction of active disease after treatment with histerelin, and Lemay *et al.* (1988b) a 54% reduction with buserelin, compared with the decrease of 34% in our study. This difference may, at least in part, be attributed to the higher active score before treatment in our patients.

In this study all women had complete remission of endometriosis-associated symptoms within 4 months of the start of therapy.

The side effects reported during treatment appear to be related to oestrogen deprivation. The prevalence of side effects in this series is comparable to the one reported by other investigators (Shriock *et al.* 1985; Steingold *et al.* 1987; Lemay *et al.* 1988a; Lemay *et al.* 1988b), and these effects were well tolerated by the patients.

The ovarian epithelial cell membrane antigen CA 125 has been found to be increased in patients with endometriosis (Barbieri *et al.* 1986; Patton *et al.* 1986; Pittaway & Fayez 1986; Fedele *et al.* 1988). All authors agree that, although the specificity of this test is high, its low sensitivity precludes its use in screening patients for endometriosis. So far, few studies have assessed the value of CA 125 estimations in the follow-up of patients with endometriosis. Pittaway & Fayez (1986) reported that CA 125 values correlated with the clinical course in 84% of women with endometriosis treated with operative laparoscopy or laparotomy with, or without, 2–3 months of postoperative danazol (600 mg to 800 mg daily). Kauppila *et al.* (1988) reported that danazol or surgical elimination of endometriosis significantly decreased CA 125 levels, whereas medroxyprogesterone acetate did not, although danazol and medroxyprogesterone acetate were equally effective in inducing regression of the disease; however, the CA 125 changes during medical treatment did not correlate with the clinical response.

In our series, at the time of diagnostic laparoscopy, we found a correlation between total and active AFS scores for endometriosis and CA 125 plasma levels, but not between adhesion scores and this marker. Such correlations were not found at second look laparoscopy after 6 months of therapy with a LHRH analogue.

There was a correlation between a decrease in AFS score and a decrease of >40% in CA 125 level in only seven of the 22 women (32%). Four of the five women who scored worse at second-look than at diagnosis showed a significant decrease in CA 125 plasma levels, as did one of the two women who had no difference in AFS score before and after medical treatment with buserelin.

We therefore conclude that CA 125 plasma levels are proportional to the extent of the disease at diagnosis, but the determination of CA 125 has no value in monitoring medical treatment efficacy. Laparoscopy remains the optimum standard for both diagnosis and follow-up of patients treated for endometriosis

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The use of rectus abdominis myocutaneous flaps following excision of vulvar cancer

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Summary. Rectus abdominis myocutaneous flaps have been used in 16 women following radical excision of extensive vulvar cancer. In two women the procedure was part of the primary surgery, in 11 for recurrence of vulvar cancer and in three for symptomatic palliation. Fifteen (94%) of the grafts took with primary healing. Thirteen of the 16 patients are alive 6–60 months (median 29 months) after surgery and the three who died benefited from symptomatic palliation. Simultaneous vulvar reconstruction allows good cosmetic rehabilitation and is an important part of the armametarium for the management of patients with advanced primary or recurrent vulvar carcinoma. This technique offers excellent surgical clearance of massive offensive and painful vulvar tumours.

Although there is a trend towards more conservative treatment of *in situ* carcinoma and microinvasive carcinoma of the vulva, many patients still present with advanced disease which requires radical surgery (Fig. 1) (DiSaia & Creasman, 1989). Recent preliminary reports indicate that combined radiotherapy and chemotherapy may contribute to enhanced locoregional control in advanced or recurrent disease, and may allow lesser surgery with preservation of normal anatomy in selected cases (Thomas *et al.* 1989) Although we have promising results using this approach with or without surgery (unpublished data) to treat this last group of patients, sometimes radical palliative surgery is the only option to relieve the unbearable symptoms which also may present great nursing difficulty. Cavanagh & Shepherd (1982) showed that in selected primary and recurrent stage IV tumours of the vulva, ultraradical exenterative surgery may be warranted. This can be explained by the fact that vulvar cancer is commonly indolent, extends slowly and metastasizes fairly late (DiSaia & Creasman 1989). Over half of the recurrences are local, near the site of the primary lesion and can often be treated successfully by local excision and/or interstitial radiation (Simonson 1984; Prempree & Amornmarn 1984)

Most radical vulvectomy operations or wide local excisions of recurrences can be closed primarily or with the assistance of Z-plasty pedicle flaps (Julian & Woodruff 1974). However, there are occasional perineal resections which are so extensive that neither technique is adequate for primary closure. In these cases the myocutaneous flap can be used to cover the resulting large denuded areas. Various musculocutaneous grafts have been described for this purpose including the gracilis, rectus abdominis, tensor

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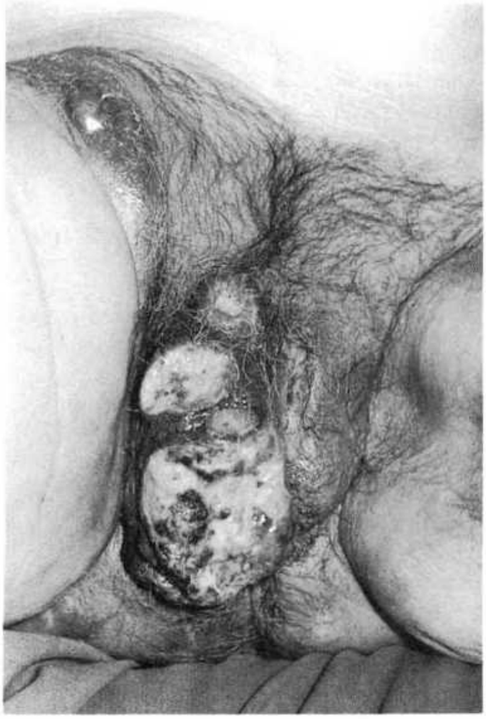

Fig. 1. A 72-year-old woman presenting with an extensive recurrent moderately differentiated squamous carcinoma of the vulva and fungating metastatic groin nodes. As the lesion was extremely painful, foul smelling and bleeding, she underwent a palliative resection of the tumour with grafting of the vulva and groin.

fascia lata, gluteus maximus and lattisimus dorsi flap (Bostwick *et al.* 1979; Morrow *et al.* 1979; Nahai *et al.* 1979; Berek *et al.* 1983; Logan *et al.* 1984; Taylor *et al.* 1984; Kennedy *et al.* 1987). We now present the first follow-up study of the use of rectus abdominis myocutaneous grafts following radical resection of vulval cancer.

Patients and methods

The charts of all 16 patients who had a perineal reconstruction with a rectus abdominis myocutaneous graft at the Royal Marsden and St. Bartholomew's Hospitals during the last 6 years were reviewed. Their ages ranged from 25 to 77 years (mean 55 years). They have been followed up for 4 to 72 months (median 29 months) after surgery.

Two patients had surgery for large fungating stage III tumours. One of them also had a malignant sinus in to the right buttock. Both underwent radical vulvectomy with bilateral groin lymphadenectomy and the second patient in addition had a pelvic lymphadenectomy. The second group of 14 patients had surgery and grafting for recurrent vulvar cancer: in 11 patients the operation was intended to be curative and in three palliative. Seven of these patients underwent pelvic exenteration (four anterior, two posterior and one total), four had radical vulvectomy and three had a wide local excision. Most of these patients had been treated earlier for recurrent vulvar cancer: ten had previously undergone one or more wide local excisions, 11 radiotherapy and four chemotherapy for their recurrence. The three patients who underwent a palliative procedure had very painful large fungating tumours producing foul smelling discharge and bleeding. They had an extremely poor quality of life and with full informed consent they accepted that surgery was the only option available to relieve their symptoms as they had all received previous radiotherapy elsewhere.

Surgical technique

The patient is positioned in the Lloyd-Davis position. A dual approach is adopted with the reconstruction immediately following the surgical resection of the tumour. Multiple sections of the resection margins are sent for frozen section in order to confirm complete surgical clearance of the tumour. As the success of the grafting procedure is completely dependent on the identification and preservation of the deep inferior epigastric vascular pedicle, it is essential that the surgeon is familiar with the anatomical relations pertinent to this procedure. The flap is marked overlying the rectus abdominis muscle. Taking care not to undercut the cutaneous portion of the flap, the anterior rectus sheath is incised cranially (Fig. 2), sweeping caudally until the neurovascular bundle is identified. Once the deep inferior epigastric pedicle is located the rectus muscle and overlying skin can be elevated as a unit. The posterior rectus sheath is elevated with the flap. Then the flap is introduced through a generous subcutaneous tunnel between the abdominal incision and the perineal defect, carefully avoiding rotation of the pedicle (Fig. 3). The tunnel must be of adequate size to prevent any constriction. If an exenteration is performed the pelvic floor is covered with an omental sling. The abdomen is closed by a mass closure technique with Number 1 looped Nylon or PDS. The vulvar skin is closed with inter-

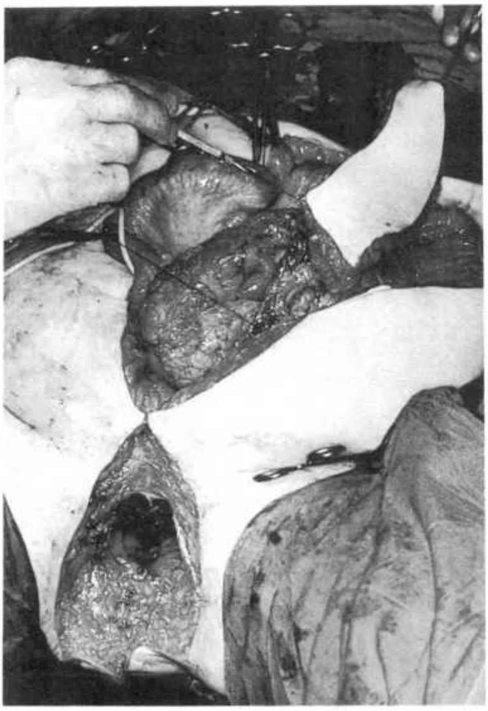

Fig. 2. Taking care not to undercut the cutaneous portion of the flap, the anterior rectus sheath is incised cranially, sweeping caudally until the neurovascular bundle is identified.

rupted stitches and staples are used for the abdominal wound (Fig. 4). After exenteration the pelvis is drained with a Robinson drain. The abdominal and pelvic wounds are drained with Portovac suction drains. Perioperative prophylactic antibiotics (cefuroxime and metronidazole) were given and women were mobilized early after surgery. The grafts were inspected every day for skin edge necrosis. If necessary the skin was trimmed and refashioned.

Results

Fifteen of the 16 grafts took with primary healing. In one, the rectus abdominis myocutaneous flap necrosed within the first postoperative week, probably due to an insufficient vascular pedicle in a 78-year-old woman with known cardiovascular disease. The flap was removed and the defect successfully closed with a tensor fascia lata myocutaneous graft. In two other patients a small segment of the graft was lost, which did not require any secondary grafting. Morbidity due to the radical surgery was minimal as is outlined in Table 1. The average stay in hospital after surgery was 31 days (range 24–71). There were no perioperative deaths. The three patients who underwent palliative surgery died 4, 8 and 9 months postoperatively with widespread distant metastatic disease. However, they benefited from satisfactory palliation of their local symptoms. The other 13 patients (81%) are alive 6–72 months (median 29 months) after surgery. Two of them (12%) proved to have metastatic disease (one metastasis in the piriformis muscle 12 months postoperatively, and one brain metastasis 10 months postoperatively treated with radiotherapy). Two further patients (12%) had a local recurrence in the margin of the myocutaneous graft (3 and 15 months postoperatively) and required further wide local excision. The five younger women have functional vaginas and are sexually active. One is trying to conceive and if successful hopes for a vaginal delivery. None of the patients showed any evidence of an incisional hernia of the abdominal wound.

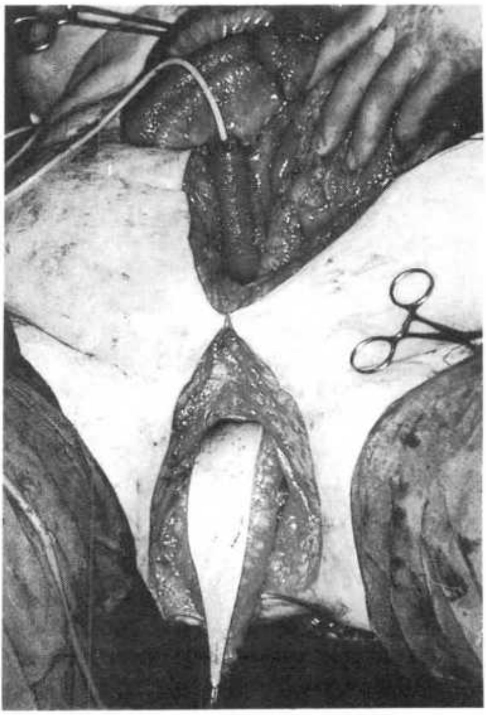

Fig. 3. The flap is introduced through a generous subcutaneous tunnel between the abdominal incision and the perineal defect. As the patient underwent an anterior exenteration to obtain adequate clearance of the tumour, one can see the ileal conduit which has been catheterized.

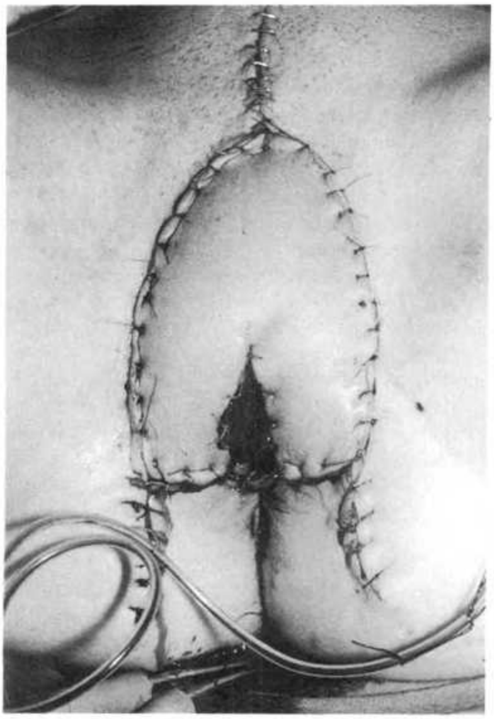

Fig. 4. Grafted vulva immediately postoperatively showing the healthy rectus abdominis myocutaneous graft, a patent vagina and the Portovac suction drainage of the perineal wound.

Discussion

Great progress has been made in vulvar reconstruction after radical surgery and many techniques are now available to restore normal anatomy in these patients. A split thickness skin graft (STSG), which is a free skin graft completely detached from the donor site, is used primarily to cover skin defects where there was little or no loss of subcutaneous tissue, such as after skinning vulvectomy. However, a STSG can have only a limited success if the recipient area is immediately overlying bone or has been previously irradiated. In gynaecology, rotational flaps or transposition flaps are most commonly used to cover extensive full-thickness defects on the vulva, groin or perianal region after radical surgery (Julian *et al.* 1974; Barnhill *et al.* 1983; Gusberg *et al.* 1988). They contain skin, underlying subcutaneous tissue, and occasionally the deep fascia and can be derived from adjacent vulvar, perineal, buttock or thigh skin. However, the 1:1·5 restriction of width to length with cutaneous flaps limits their use around the pelvis. The cutaneous rotational flap particularly is not very reliable (Stern and Lacey 1987). The principle that the skin can be moved together with the underlying muscle was first used in the reconstruction of the cheek using a sternomastoid myocutaneous flap (Owens 1955). Since their introduction to gynaecology by McCraw *et al.* (1976), myocutaneous flaps have been widely used for vulvar, vaginal and pelvic reconstruction (Bostwick *et al.* 1979; Morrow *et al.* 1979; Nahai *et al.* 1979; Wheeless *et al.* 1979; Berek *et al.* 1983; Logan *et al.* 1984; Taylor *et al.*1984; Lacey *et al.*1988; Cain *et al.* 1989; Lilford *et al.* 1989). Myocutaneous grafts are required when very large defects need to be covered or when the vulva has been irradiated previously. They are very suitable for this because of a wide arc of rotation and transfer of an island of skin rather than a broad-based pedicle. In addition, myocutaneous flaps also bring a new blood supply to the recipient wound, which has often been devascularized by previous radiotherapy or surgery (McCraw *et al.* 1977). Circumstances influencing choice of graft include size, contour, depth of the deformity, proximity of the deformity to the potential donor site, presence of necrosis and infection and the requirement of a new blood supply (Stern & Lacey 1987). In some situations, it is necessary to use several reconstructive procedures simultaneously, or serially, to achieve optimal reconstruction.

Radical and extensive excision with rectus abdominis grafting of primary advanced and recurrent vulvar cancers in selected cases offers excellent surgical removal of these massive off-

Table 1. Complications related to the grafting procedure and to radical surgery in the 16 women undergoing radical excision of vulvar cancer with a simultaneous rectus abdominis myocutaneous flap operation

Myocutaneous flap operation.

1. Loss of the entire flap secondary to insufficient dominant vascular pedicle requiring a tensor fascia lata graft (one patient).
2. Loss of a small segment of the flap (about 2 × 2 cm) not requiring grafting (two patients).

Radical surgery

1. Pulmonary embolus successfully medically treated (one patient).
2. Deep venous thombosis (one patient).
3. Urinary tract infection (three patients).
4. Groin abcess requiring draining (one patient).

ensive and painful tumours. Allowing that most of the patients in this series had received extensive treatment previously, the overall and disease-free survival is excellent. The technique should be reserved for those in whom extensive perineal resection is required to provide adequate clearence of the primary carcinoma or recurrence.

At the same time release of severe perineal contractures and adequate excision of previously heavily irradiated perineal tissue may be achieved. Distant metastasis is in our opinion a relative contraindication for this type of radical surgery. However, on occasions the palliative excision of large and painful lesions may be indicated, not only to obtain symptomatic relief but also to allow easier nursing and personal hygiene.

The use of the rectus abdominis myocutaneous graft for vulvar reconstruction allows early mobilisation and has a low morbidity. The rectus abdominis myocutaneous flap is an exceptionally versatile flap and allows movement of a large segment of skin with the rectus muscle to the groin or perineal area (Logan & Mathes 1984). It has the advantage over other flaps that the scars can be hidden under normal clothing or a bathing suit. This is particularly important for the cosmetic rehabilitation of younger women where the psychosexual effects from radical gynaecological surgery can be severely disabling.

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Second trimester pregnancy termination using extra-amniotic ethacridine lactate

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Abstract

Objective—To investigate the efficacy of ethacridine lactate by the extra-amniotic route for second trimester pregnancy termination and its associated complications.
Design—Retrospective study of women undergoing second trimester termination, over 3½ years, with extra-amniotic ethacridine alone, or extra-amniotic ethacridine supplemented later by extra-amniotic 15-methyl prostaglandin $F_2\alpha$.
Setting—Teaching hospital in Bombay.
Patients—315 consecutive women undergoing late abortions with extra-amniotic ethacridine. Demographic features were similar in the two groups.
Interventions—In group 1, 207 women had 150 ml of 0·1% ethacridine lactate injected slowly into the extra-amniotic space. In group 2, 108 women had the initial injection supplemented 6 h later by an extra-amniotic injection of 250 μg (1 ml) of 15-methyl prostaglandin $F_{2\alpha}$
Main outcome measures—The occurrence of abortion following the induction procedure. The development of complications such as haemorrhage, infection, or injury to the uterus or cervix.
Results—The method was successful in 191 women (92%) in group 1 and in 106 (98%) in group 2. The median induction-abortion intervals were 35 and 19 h, respectively (Mann-Whitney *U* test, $P<0·001$). The corrected complication rate was <10% (30 women), with unplanned uterine evacuation in 6% (20), haemorrhage in 1% (4), and pelvic infection in 4% (14).
Conclusion—The use of extra-amniotic ethacridine lactate provides an effective and safe treatment method for second trimester legal abortion. The induction-abortion interval can be appreciably reduced by supplementary prostaglandin.

Ethacridine lactate has been used by the extra-amniotic route for second trimester pregnancy termination for over 20 years in Japan (Manabe 1969; Neubart & Schulman 1972), and more recently in Sweden (Ingemanson 1980), with favourable results.

The present study is an analysis of late abortions with ethacridine, performed at the Wadia Maternity Hospital, Bombay, to investigate the efficacy of this method and its associated complications.

These women were having second rather than first trimester abortions essentially because they presented late for the procedure. The reasons for delay in recognition of the pregnancy, or in seeking advice, included ignorance or apprehension (especially in the illiterate unmarried young primigravida), irregular menstruation, failure of contraception or of sterilization, suspicion of menopause in the older woman, and disruption of a relationship. A small number of these

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women had a fetal abnormality diagnosed by ultrasonography in the second trimester. With the available medical care system at the teaching hospital concerned, there was little delay in obtaining abortion once a decision was made to seek an abortion.

Subjects and methods

The hospital case records of all the 315 consecutive women undergoing second trimester ethacridine termination during the 3½ years between January 1986 and June 1989 were reviewed.

A 14 French gauge Foley catheter was passed through the cervix, the balloon inflated to 20 ml, and 150 ml of 0·1% ethacridine lactate (Emcredil, M.M. Laboratories, Bombay) was injected slowly into the extra-amniotic space. The end of the catheter was clamped, and the catheter left in place for about 8 h.

Extra-amniotic ethacridine was instilled in 207 women (group 1). A further 108 had the initial injection supplemented 6 h later by an extra-amniotic injection of 250 μg (1 ml) of 15-methyl prostaglandin (PG) $F_{2\alpha}$ (carboprost tromethamine, Upjohn Ltd., Sussex), diluted to 10 ml with normal saline (group 2). $PGF_{2\alpha}$ is imported in India. The variable availability of the prostaglandin and the woman's ability to pay for this drug determined whether it was used.

A vaginal examination was made if uterine activity had not started after 24 h. If the cervix was favourable, an intravenous infusion of oxytocin (5–10 units in 500 ml of 5% dextrose) was started. If the cervix was unfavourable, vaginal examinations were repeated after 12–24 h and the oxytocin infusion delayed until between 24 and 72 h. If no uterine activity was observed and the cervix was unfavourable after 72 h, the method was considered to have failed.

These women were generally given 30 mg of pentazocine lactate and 25 mg of promethazine hydrochloride intramuscularly when required for the relief of pain. After expulsion of the fetus, 0·2–0·4 mg of methyl-ergometrine maleate was given intramuscularly. Prophylactic antiobiotics (generally ampicillin and metronidazole for 7 days) were prescribed. Rh negative women were given immunoglobulin during the first 24 h following abortion Contraceptive advice was offered. The women were advised to attend the out-patient clinic in 1–2 weeks (and again later, if there was a need) for follow-up.

Complications which actually occurred in the hospital, or which were reported during the follow-up in the out-patient clinic, were recorded. The woman was considered to have pelvic infection if she had lower abdominal pain with pyrexia of 37·5°C or more, a foul vaginal discharge, tenderness or adnexal masses on vaginal examination. Blood loss of >500 ml was categorized as a haemorrhage.

The mean age of the women in group 1 was 25·6 (SD 6·7) years, and in group 2 it was 25·5 (SD 6·4) years, the difference was not significant (t-test, P=0·9). The parity of these women is shown in Table 1.

Results

The method failed in 16 women in group 1, and in 2 in group 2. Abortion was induced in them by other procedures later (reinstillation of 150 ml extra-amniotic ethacridine in nine, intra-muscular injections of 250 μg of carboprost at 2 h intervals in seven, and oxytocin drip in two) The prolonged induction-abortion intervals in these women were pooled with the results in women who aborted after the first treatment to calculate the overall induction-abortion interval. The median induction-abortion interval was 35 (range 10–156) h in group 1 (ethacridine only) and 19 (10–108) h in group 2 (ethacridine plus PG). The difference between the two groups was significant (Mann-Whitney U test, P<0·001) (Table 2).

Complete expulsion of the products of conception (clinical impression) occurred in 116 women (37%). After abortion, planned uterine evacuation was performed in 221 women (70%) either as a policy decision by the clinician on duty, or because of a clinical suspicion of an incomplete abortion.

The complications are listed in Table 2 Unplanned evacuation (on suspicion of retained products, or following haemorrhage or infection) was required in 20 women (6%). Pelvic infection occurred in 14 (4%).

The overall complication rate was 12% (38 women). Unplanned evacuation was also required in three women with haemorrhage and in five with pelvic infection. When double-counting of these subjects was excluded, the corrected complication rate was under 10%

Discussion

The action of ethacridine lactate is believed to be

Table 1. Parity of the women in the two groups

Parity	Ethacridine (group 1)	Ethacridine + PG (group 2)	Total
Nulliparous	62 (30%)	41 (38%)	103(33%)
1-3	111 (54%)	55 (51%)	166(53%)
4+	34 (16%)	12 (11%)	46 (14%)
Total	207	108	315

mechanical, not chemical (Manabe 1969; Neubart & Schulman 1972). The fetus is generally born undamaged.

The basic method using extra-amniotic ethacridine lactate and oxytocin infusion is inexpensive, and was effective in 92% of the women. Since cost is an important factor in developing countries, delaying the use of supplementary PG until after 72 h would be worthy of consideration. Whether such a small supplementary dose of carboprost (250μg) would be effective after 72 h could be determined by a further study.

The main drawback of inducing abortion with extra-amniotic ethacridine and oxytocin infusion is the prolonged induction-abortion interval (mean 42 h; median 35 h in this study). The

Table 2. Length of labour and complications with ethacridine termination of pregnancy

	Gestation at abortion (weeks)		
	13-16	17-20	All gestations
Ethacridine lactate			
No of women	103	104	207
Length of labour (h)			
Mean (SD)	44 (31)	41 (24)	42 (28)
Median	36	34	35
Range	12-149	10-156	10-156
No. where method failed (>72 h)	9	7	16
No. needing oxytocin drip	74 (72%)	84 (81%)	158 (76%)
No. having planned evacuation	73 (71%)	79 (75%)	152 (73%)
Ethacridine lactate and PG			
No. of women	52	56	108
Length of labour (h)			
Mean (SD)	26 (19)	22 (9)	24 (14)
Median	18	20	19
Range	11-108	10-60	10-108
No. where method failed (>72 h)	1	1	2
No. needing oxytocin drip	19 (37%)	24 (43%)	43 (40%)
No. having planned evacuation	31 (60%)	38 (68%)	69 (64%)
Total women treated	155	160	315
Complications			
Unplanned uterine evacuation	13 (8%)	7 (4%)	20 (6%)
Haemorrhage	2 (1%)	2 (1%)	4 (1%)
Transfusion	2 (1%)	—	2 (1%)
Pelvic infection	5 (3%)	9 (6%)	14 (4%)
Uterine/cervical injury	—	—	—
Total (with complications)	20 (13%)	18 (11%)	38 (12%)
Corrected total*	15 (10%)	15 (9%)	30 (10%)

* Subjects with haemorrhage or infection also requiring unplanned uterine evacuation.

induction-abortion interval was appreciably reduced by supplementary PG (mean 24 h; median 19 h). This overall duration of treatment needs to be compared with published results of other methods for second trimester termination. Cameron & Baird (1987) reported a mean induction-abortion interval of 17 h with extra-amniotic PGE_2 and 12 h with intra-amniotic PGE_2 and urea for mid-trimester abortion. Kerenyi (1973) reported a mean induction-abortion interval of 25 h with intra-amniotic hypertonic saline plus intravenous oxytocin and Borenstein *et al.* (1980) reported a mean interval of 25 h with intra-amniotic hypertonic saline only. More recently, in a large study from Oxford, Hill & MacKenzie (1989) have reported mean induction-abortion intervals of 15 h using intravenous oxytocin both with extra-amniotic PGE_2 and intra-amniotic PGE_2 for mid-trimester abortion.

Early supplementation with PG reduced the induction-abortion interval appreciably (Mann-Whitney *U* test, $P<0{\cdot}001$), but not the proportion needing evacuation of retained products (χ^2 $P=0{\cdot}1$) (Table 2). However, in our study, planned uterine evacuation was performed not only for clinical suspicion of an incomplete abortion, but also according to the surgeon's preference.

Our results confirm the Japanese experience that this drug generally lacks toxicity (Manabe 1969; Neubart & Schulman 1972). There were no deaths in this series.

Ethacridine lactate has antiseptic properties. The rate of infection was 4% compared with the generally reported rate of sepsis of 5–10% in all second trimester abortions (Filshie 1989).

The absence of uterine or cervical injury is gratifying. In a small Israeli study of mid-trimester abortions with much larger volumes (up to 600 ml) of 0·1% ethacridine and intravenous oxytocin, cervical injury was reported in almost 4% (Nabriski *et al.* 1971). Hill & MacKenzie (1989) reported 0·1 and 0·3% frequency of genital tract trauma with extra-amniotic PGE_2 and intra-amniotic PGE_2. The absence of uterine or cervical injury in our population may have been influenced by the large number of parous women (212, 67%) (Table 1), and by the relative absence of uterine scars from previous caesarean sections (five in group 1, none in group 2)

The complication rate was <10% ($n=30$), most complications ($n=20$) were unplanned uterine evacuations. The frequency of the more severe complications was low (Table 2). This compares favourably with the complication rates reported in the RCOG Survey on Late Abortions (>5%) (Stanwell-Smith 1984), and in the Scottish study (5%) (Cameron & Baird 1987).

Extra-amniotic ethacridine lactate is an inexpensive, effective and safe method of second trimester termination. The induction to abortion interval can be favourably influenced by supplementary PG.

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Changes in circulating alphafetoprotein following administration of mifepristone in first trimester pregnancy

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Summary. The occurrence of fetomaternal haemorrhage was investigated in 30 women by measuring maternal serum alphafetoprotein (AFP) levels before and after the administration of mifepristone (RU 486) for termination of first trimester pregnancy. A significant rise in AFP levels was seen in 21 women (70%), the increase ranging from 6 to 660% of baseline levels. The apparent frequency of fetomaternal haemorrhage was similar to that reported previously for surgical termination of first trimester pregnancies.

It is well-known that invasive diagnostic procedures in the first half of pregnancy, such as chorion villus sampling and amniocentesis, may be associated with increases in maternal blood alphafetoprotein (AFP) (Chard *et al.* 1976, Mariona *et al.* 1986, Ward *et al.* 1985, Warren *et al.* 1985, Knott *et al.* 1988). The rise in AFP is due to fetomaternal haemorrhage: fetal levels of AFP are around a million-fold greater than maternal levels so that transfer of very small quantities of fetal blood can produce this phenomenon. Fetomaternal haemorrhage can also occur in association with elective termination of pregnancy (Katz 1969, Queenan *et al.* 1971, Voigt & Britt 1969, Naik *et al.* 1988).

Mifepristone (RU 486) is a synthetic 19-norsteroid which binds to the progesterone receptor and therefore acts as an antagonist to the effects of progesterone on target cells (Baulieu 1985a, b, Shaison *et al.* 1985). It is active when given by mouth and has a half life of 24 h (Swahn *et al.* 1985). A number of studies have demonstrated that it can prevent both the initiation and progression of pregnancy in the first 9 weeks (Baulieu & Ullman 1986). Some 60–85% of women abort completely with mifepristone alone (Kovacs *et al.* 1984, Couzinet *et al.* 1986), increasing to nearly 100% when it is used in combination with the prostaglandin analogue 16,16-dimethyl-trans-2-PGE$_1$ (gemeprost) (Cameron *et al.* 1986, Rodger & Baird 1987).

In the present study we demonstrate a striking increase in maternal serum AFP levels after administration of mifepristone, with little or no further increase after administration of prostaglandin

Subjects and methods

The study population was the same as that described previously as part of an investigation of the effects of mifepristone on hormone levels in early pregnancy (Olajide *et al.* 1989; Howell *et al.* 1989). Thirty women presenting for elective first trimester termination of pregnancy were recruited for the study. All fulfilled one or more criteria for termination of pregnancy under the 1967 Abortion Act, and informed consent was obtained. All women were <9 weeks pregnant as assessed by the last menstrual period, pelvic examination and ultrasound scan and had no

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pregnancy complications. A single oral dose of 600 mg of mifepristone (Roussel-Uclaf) was given. Blood (10 ml) was taken immediately before and then at hourly intervals for 4 h. Pulse, blood pressure, temperature and any side-effects were noted, then the women returned home. After 48 h they returned and a pelvic ultrasound was performed before a vaginal pessary containing 1 mg of gemeprost (Cervogem, May & Baker) was inserted. Blood samples were taken before insertion of the vaginal pessary and at 2-h intervals afterwards for 4 h. The women left hospital after 48 h and were examined once a week for the next 4 weeks. The completeness of the abortion was assessed by a scan at 1 week. At each visit side-effects were noted and further blood samples collected.

All blood samples were separated and the serum stored at −20°C until assayed. The radioimmunoassay (RIA) for AFP has been described previously (Kitau *et al.* 1988).

Results

All women bled within 2–4 h following gemeprost. The abortions were complete with no clinical or ultrasound evidence of retained products 1 week later. Two women had moderate vaginal bleeding for 24 h after the abortion. No unusual side effects were reported Following administration of gemeprost, some women experienced nausea and vomiting. All had lower abdominal cramps, but only five required analgesia. There was no significant change in AFP levels in the 4 h following administration of mifepristone. However, 2 days later, before the administration of gemeprost, 21 of the 30 women showed a rise in their serum AFP to levels >2SD above the mean of the control values. The increases ranged from 6% to 660% (median 87%). The findings in the first 10 women are shown in Fig. 1.

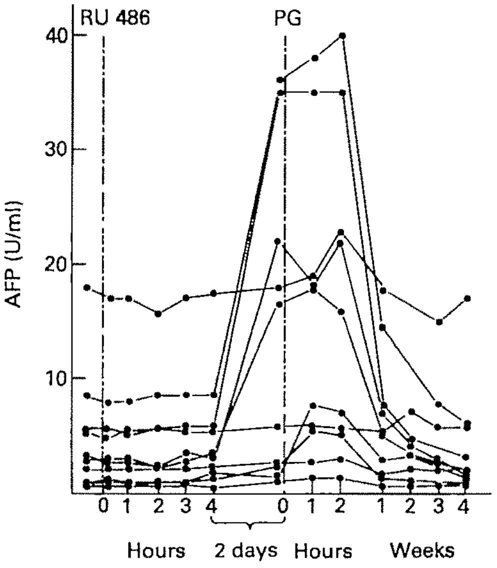

Fig. 1. Levels of circulating alphafetoprotein (AFP) in 10 women after the administration of mifepristone (RU 486) and gemeprost (PG) for termination of first trimester pregnancy

The existence or extent of the rise in AFP bore no obvious relation to the stage of pregnancy or to the interval between mifepristone administration and the commencement of bleeding.

Discussion

The mechanism of the contragestive action of mifepristone is not fully understood (Baulieu & Ullman 1986). The primary action is believed to be blockade of the action of progesterone at the receptor level In association with this mifepristone causes necrosis of the endometrium and decidua in early pregnancy (Herrman *et al* 1982). Studies of placental function *in vitro* have shown reduced secretion of hCG, hPL and progesterone by mifepristone in cultured syncytiotrophoblast (Das & Catt 1987). Inhibition of hCG production, but not hPL, has also been observed in trophoblastic explants (Bischof *et al.* 1986). However, no short-term changes in the circulating levels of trophoblast products have been shown during administration *in vivo* (Couzinet *et al.* 1986, Howell *et al.* 1989, Olajide *et al.* 1989), although levels fall as soon as the conceptus is delivered.

The present findings confirm earlier observations to the effect that fetal blood (or other products) may enter the maternal circulation during elective termination of first-trimester pregnancy (Katz 1969, Queenan *et al.* 1971, Voigt & Britt 1969, Naik *et al.* 1988). However, these studies were all based on mechanical procedures for termination. It might be anticipated that the pharmacological process associated with administration of mifeprestone would be less likely to cause fetomaternal haemorrhage and that the increase in maternal serum AFP, if any, would occur during the expulsive contractions induced by prostaglandin. However, the present study shows that the frequency of this rise (70%) is similar to that previously reported for surgical termination of first trimester pregnancy (58%) (Naik *et al.* 1988), and that it occurs *before* the administration of prostaglandins.

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Regional differences in vascular responses in the human uterus

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Summary. Tissue specimens from the fundus, isthmus and distal cervix were obtained from 14 women at hysterectomy at various phases of the menstrual cycle. Ring preparations of small intramyometrial and intracervical arteries were dissected and mounted in organ baths; isometric tension was recorded and responses to contractile agents were studied. The amplitude of responses to K^+ (124 mmol/l) of the vessel preparations ranked fundus $\geqslant$ isthmus $>$ cervix. While similar pD_2 values for noradrenaline (NA) were found, the E_{max} values ranked cervix $\geqslant$ isthmus $\geqslant$ fundus (cervix $>$ fundus). The pD_2 values for arginine-vasopressin (AVP) showed minor differences, while the E_{max} values for this peptide ranked fundus $\geqslant$ isthmus $\geqslant$ cervix (fundus $>$ cervix). Arteries from the fundus and isthmus displayed weak, inconsistent contractile responses to prostaglandin $F_{2\alpha}$, but more pronounced contractions were induced by this prostanoid in arterial preparations from the distal cervix. The results suggest regional differences in vascular mechanical responses to endogenous vasoactive agents in the human uterus.

The human uterine cervix and body show marked differences in composition and mechanical properties (Uldbjerg 1989). In addition, the individual uterine tissue elements may display regional variations in functional characteristics. Thus, prostanoids such as PGE_2 produce different effects on isolated myometrial smooth muscle from uterine isthmus, fundus and the uterotubal junction (Wiqvist *et al.* 1983). Moreover, the factors affecting medial smooth muscle activation in the uterine vascular bed differ. The adrenergic neuronal supply is more dense in cervical tissue than in the uterine body (Owman *et al.* 1967) and the uterine vessels are also influenced by local prostaglandin synthesis, which may show regional variations (Uldbjerg *et al.* 1987). Furthermore, the uterus contains tissue levels of vasopressin that exceed the plasma levels and large quantities of this peptide have been found in the cervix (Lundin *et al.* 1989).

Uterine arteries seem to change in functional characteristics as they enter the myometrium and decrease in dimension (Maigaard *et al.* 1985). However, whether regional differences in medial smooth muscle responses to vasoactive agents add further to the individual characteristics of the uterine vascular bed is not known. In

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the present study we have compared the effects of noradrenaline (NA), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and arginine vasopressin (AVP) on similar size human intramyometrial and intracervical arteries isolated from the fundus, isthmus and distal part of the cervix.

Subjects and methods

From the uteri of 14 women who underwent hysterectomy at various phases of the menstrual cycle, macroscopically normal myometrial tissue specimens were cut from the fundus, isthmus and distal cervix The women ranged in age from 36 to 51 years (mean 44 years) and in parity from 1 to 3. Six were in the proliferative phase and eight in the secretory phase of the menstrual cycle. The indications for hysterectomy were menorrhagia in one, metrorrhagia in seven and uterine fibromyomata in the other six. None of the patients received any hormonal treatment. The specimens were immediately transferred to a 4°C Krebs solution, and transported to the laboratory. Under a stereo microscope (Kyowa) 0·8–1·2 mm tubal segments of intramyometrial arteries were isolated by microdissection. The internal diameters of the arteries were 291 (SEM 16) μm in fundal vessels, 250 (SEM 14) μm in isthmic vessels and 236 (SEM 15) μm in intracervical arteries ($n=14$, no significant differences). The vessels were transferred to 5 ml organ baths containing Krebs solution (37°C) perfused with carbogen, resulting in a pH of 7·40 ± 0·05, and were mounted as ring preparations between two opposing L-shaped hooks (Högestätt *et al.* 1983). One of the hooks was connected to a transducer (Grass FT03), and the other to a moveable sledge which allowed fine adjustments of tension in the preparations. Isometric tension was recorded and displayed on a Beckman R611 or a Grass model 7D polygraph. The preparations were allowed to equilibrate for 1–2 h and passive tension of the arteries was set at 4 mN/mm by repeated adjustments At this basal tension level near maximum mechanical responses to K^+ (124 mmol/l) were obtained. The bath solution was replaced at least every 20 min. Contractions were elicited by a high K^+-solution until reproducible (less than 10% difference between two subsequent contractions). Only preparations fulfilling this criterion were accepted for further experiments.

All responses to drugs were measured as the amplitude (mN) achieved from the initial baseline and expressed as mN per mm length of the preparations (mN/mm).

The maximum contractile effect (E_{max}) and the drug concentration producing half maximum response (EC_{50}) were determined in each experiment. The means of E_{max} and $pD_2=-\log(EC_{50})$ were assessed from the individual experiments and given as the mean (SEM) value. Significance of difference was initially assessed by a one-way analysis of variance after ascertaining homogeneity of variance. Thereafter, if appropriate, the difference between group means was assessed by the two-tailed *t*-test for groups of non-paired observations with a P value of $<0·05$ considered significant. Comparisons between vessels from different regions and between the various agonists were performed in preparations from the same patients ($n=8$). The effects of cocaine pretreatment on responses to noradrenaline were studied in separate experiments in preparations from six further women.

Solutions

Normal Krebs (mmol/l): NaCl 119, KCl 4·6, $NaHCO_3$ 15, $CaCl_2$ 1·5, $MgCl_2$ 1·2, NaH_2PO_4 1·2, glucose 11.

High K^+ Krebs (mmol/l): KCl 124, $NaHCO_3$ 15, $CaCl_2$ 1·5, $MgCl_2$ 1·2, NaH_2PO_4 1·2, glucose 11.

Drugs

Noradrenaline (NA, noradrenaline bitartrate, Sigma), arginine vasopressin (AVP, 8-Arginine Vasopressin, Sigma), $PGF_{2\alpha}$ (Dinoprost Upjohn), cocaine (Ph.Eur).

Results

None of the preparations investigated exhibited spontaneous contractile activity. In all types of vessel K^+ (124 mmol/l) depolarization induced an initial fast rise in tension which continued into a tonic contraction with higher amplitude. The maximum tension differed, being 11·3 (SEM 0·7) mN/mm in arterial preparations from the uterine fundus ($n=14$), 9·3 (SEM 0·8) mN/mm in arteries from the isthmus ($n=14$) and 6·3 (SEM 0·6) mN/mm in intracervical arteries ($n=14$) (difference significant between vessels from fundus and cervix, $P<0·01$). No correlation between menstrual phase and mechanical vascular responses could be demonstrated.

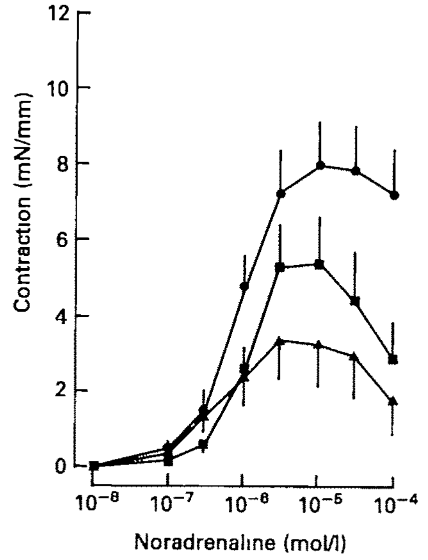

Fig. 1. Contractile responses to noradrenaline in isolated arteries from the human uterine fundus (▲), isthmus (■) and distal cervix (●). Mean (SEM), $n=8$.

Effects of noradrenaline

Noradrenaline (10^{-8}–10^{-4} mol/l) evoked concentration-related contractions in all types of vessel tested (Fig. 1). While similar pD_2 values were found, the E_{max} levels differed and ranked for the arterial preparations cervix > isthmus > fundus (Table 1). Pretreatment with cocaine, 10^{-6} mol/l, did not change concentration-response relations for noradrenaline in any of the vessels tested ($n=6$).

Effects of arginine vasopressin

Arginine vasopressin (3×10^{-12}–10^{-8} mol/l) produced concentration-dependent contractile responses with the pD_2 values ranking the vessels cervix ≥ isthmus = fundus (Fig. 2). The E_{max} values ranked fundus ≥ isthmus ≥ cervix (fundus > cervix, Table 2).

Table 1. Responses to noradrenaline in isolated arteries from the uterine fundus, isthmus and cervix†

	pD_2 (SEM) (–)	EC_{50} (mol/l)	E_{max}(SEM) (mN/mm)	
Cervix	6·12 (0·08)	$7{\cdot}6\times10^{-7}$	8·11 (1·2)	*
Isthmus	6·08 (0·08)	$8{\cdot}3\times10^{-7}$	5·59 (1·2)	
Fundus	6·29 (0·13)	$5{\cdot}1\times10^{-7}$	3·75 (0·1)	

†Maximum contractile effects E_{max} and drug concentrations producing half maximum responses EC_{50} ($pD_2=-\log EC_{50}$). Mean (SEM), $n=8$. *$P<0{\cdot}05$.

Effects of $PGF_{2\alpha}$

While $PGF_{2\alpha}$ (10^{-6}–10^{-4} mol/l) induced concentration-dependent contractile responses in intracervical arteries, vessels from the other uterine locations displayed inconsistent, weak or no responses to the prostanoid (Fig. 3). pD_2 values could not be assessed in preparations from fundus and isthmus (Table 3). The E_{max} levels for the vessel preparations ranked cervix > fundus > isthmus.

Discussion

The factors involved in activation of contraction in vascular smooth muscle show marked variation depending on the vascular bed and size of vessel in question. The present study showed that within the human uterus differences also exist between vessels of similar dimensions from different locations within the organ. Contractile responses to high K^+-depolarization probably involve calcium entry through membrane channels sensitive to changes in membrane potential (Bolton 1979). Depending on the significance of these mechanisms and the subsequent intracellular events which add to the rise in intracellular calcium concentration needed to activate the contractile proteins, varying responses to high K^+ are produced in different tissues. In the

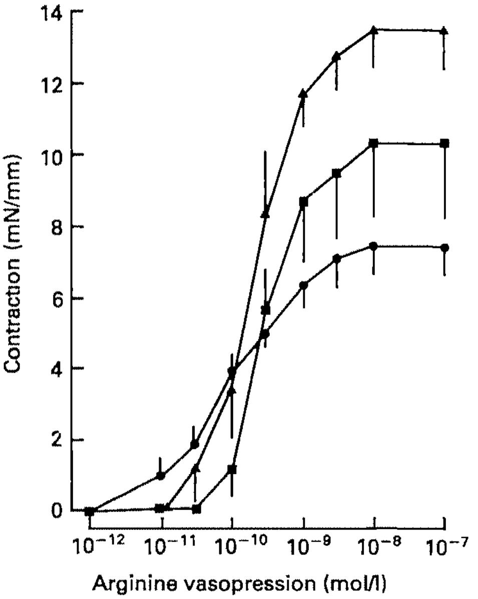

Fig. 2. Contractile responses to arginine vasopressin in isolated arteries from the human uterine fundus (▲), isthmus (■) and distal cervix (●) Mean (SEM), $n=8$

Table 2. Responses to arginine vasopressin in isolated arteries from the uterine fundus, isthmus and cervix†

	pD$_2$(SEM) (–)		EC$_{50}$ (mol/l)	E$_{max}$(SEM) (mN/mm)	
Cervix	10·23 (0·21)	*	5·9×10^{-11}	7·46 (0·8)	*
Isthmus	9·70 (0·09)		2·0×10^{-10}	10·40 (2·1)	
Fundus	9 82 (0·18)		1·5×10^{-10}	13·48 (1·0)	

†Maximum contractile effects E$_{max}$ and drug concentrations producing half maximum responses EC$_{50}$ (pD$_2$=−logEC$_{50}$). Mean (SEM), n=8 *P<0 05

present study, K$^+$-depolarization produced higher responses in intramyometrial arteries from the fundus than in vessels from the distal cervix, with intermediate values for isthmic arteries. The vessels studied showed similar dimensions and the finding could not be ascribed to non-specific damage caused by the dissection technique as no uniform pattern was found for the subsequent E$_{max}$ values for noradrenaline, arginine vasopressin and PGF$_{2\alpha}$. Thus, the results presented might reflect regional differences in the cellular response to membrane depolarization in human uterine vessels.

Whereas the human cervix and oviduct receive abundant sympathetic innervation, adrenergic nerve terminals are more scanty in the corpus and fundus (Owman *et al.* 1967) The present study showed that further regional differences exist in the vascular smooth muscle responses to noradrenaline.

Although similar pD$_2$ values were found, the E$_{max}$ values for noradrenaline showed marked variations with the highest values in arteries from the distal cervix and lower levels in isthmic and fundal arterial preparations. Such differences might add to regional variations in sympathetic neurovascular function in the human uterus.

Immunoreactive arginine vasopressin has been localized in a number of peripheral tissues (Wathes 1984; Clements & Funder 1986) including the ovary and oviduct (Schaeffer *et al.* 1984) and tissue levels that markedly exceeded the concentrations expected from plasma levels were recently demonstrated in human myometrium and cervix (Lundin *et al* 1989). These tissue concentrations (10^{-10} mol/l) correspond well to the EC$_{50}$ values obtained in the present study. An arginine vasopressin-like peptide has been demonstrated in sympathetic nerve terminals (Hanley *et al.* 1984) but the origin and exact localization of the compound in the human genital tract remains to be established. In the present study arginine vasopressin potently induced contraction in all vessels tested, without major differences in EC$_{50}$. Arteries from the uterine fundus showed the highest E$_{max}$ values, with lower levels in isthmic and cervical arteries. It has previously been suggested that arginine vasopressin may be involved in control of myometrial contractile activity and in the pathogenesis of dysmenorrhea (Åkerlund & Andersson 1976; Åkerlund *et al.* 1976; Strömberg *et al.* 1984). Taken together, the present results and the tissue levels of immunoreactive arginine vasopressin support a role for this peptide also in

Table 3. Responses to prostaglandin F$_{2\alpha}$ in isolated arteries from the uterine fundus, isthmus and cervix.

	pD$_2$(SEM) (–)	EC$_{50}$ (mol/l)	E$_{max}$(SEM) (mN/mm)	
Cervix	5·53 (0·11)	3 0×10^{-6}	6·16 (1·3)	*
Isthmus	(–)	(–)	(0·29 (0·2))	
Fundus	(–)	(–)	(1·00 (0·5))	

†Maximum contractile effects E$_{max}$ and drug concentrations producing half maximum responses EC$_{50}$ (pD$_2$=−log EC$_{50}$) are shown for cervical arteries, while only E$_{max}$ values are shown for vessels from fundus and isthmus due to the weak, inconstant responses to the prostanoid in these vessels Mean (SEM), n=8 *P<0·05

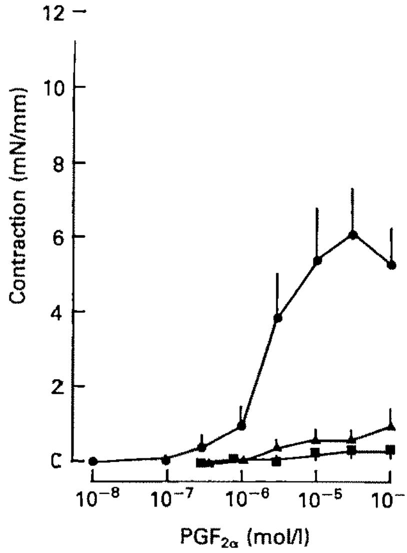

Fig. 3. Contractile responses to prostaglandin F$_{2\alpha}$ (PGF$_{2\alpha}$) in isolated arteries from the human uterine fundus (▲), isthmus (■) and distal cervix (●) Mean (SEM). n=8

control of myometrial vascular contractile activation and blood flow.

Myometrial hypercontractility in dysmenorrhea seems to involve enhanced endometrial production of $PGF_{2\alpha}$ with subsequent activation of the myometrium (Lundström & Green 1978). $PGF_{2\alpha}$-induced vasoconstriction has also been implicated in the syndrome (Wilhelmsson *et al.* 1981) but our results support previous findings (Maigaard *et al.* 1985) that $PGF_{2\alpha}$ evokes weak, inconsistent responses in myometrial vessels. These results raise doubt about a role for $PGF_{2\alpha}$-induced myometrial vasoconstriction in the primary dysmenorrhea syndrome. In small arteries from the mid-cervix, $PGF_{2\alpha}$ was previously shown to produce inconsistent responses of low amplitude (Allen *et al.* 1988), in parallel to our findings in isthmic and fundus arteries. By contrast, we demonstrated more pronounced contractile effects of $PGF_{2\alpha}$ in small arteries from the most distal cervix. Thus, vascular responses to the compound might vary within the region.

Our study on small arteries isolated from the human uterine fundus, isthmus and distal cervix has demonstrated regional variations in contractile responses to the endogenous vasoactive agents naradrenaline, arginine vasopressin and $PGF_{2\alpha}$. Such variations might add to differences in the mechanisms involved in control of regional uterine blood flow.

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Increase in plasma prorenin during the menstrual cycle of a bilaterally nephrectomized woman

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Summary. To investigate the origin of the prorenin peak that occurs during the normal menstrual cycle, plasma levels of prorenin, renin, oestradiol, progesterone, LH and FSH were measured serially in a nephrectomized woman having regular haemodialysis. The prorenin peak coincided with the LH surge and preceded the rise of progesterone, whereas renin was below the detection limit during the whole cycle. These findings indicate that the rise in prorenin during the menstrual cycle is not of renal origin but is probably due to increased production by the ovary and supports the increasing evidence for the existence of a local renin-angiotensin system in the ovary.

Prorenin is an enzymatically inactive precursor form of renin. Under normal conditions the plasma level of prorenin is about 10 times higher than that of renin itself (Sealey *et al.* 1980; Schalekamp & Derkx 1981). The kidney is by far the most important, if not the only, source of renin in plasma but a substantial proportion of the prorenin in plasma is of extra-renal origin. The ovary has been suggested to be the main source of the grossly elevated (4–6 times normal) plasma prorenin in pregnant women (Sealey *et al.* 1985*a*; Derkx *et al.* 1986) and in women who are hyperstimulated with human menopausal and human chorionic gonadotrophin (Itskovitz *et al.* 1987; Derkx *et al.* 1987). Prorenin levels in the ovarian venous effluent were found to be more than those in peripheral blood (Paulson *et al.* 1988). It is possible that the ovary is also the source of the modest increase in plasma prorenin that occurs during the normal menstrual cycle (Sealey *et al.* 1985b). This increase of prorenin follows the FSH/LH surge by about 8–16 h, suggesting that the production of prorenin is under gonadotrophic control (Sealey *et al.* 1985b). It is possible that FSH or LH, or both, stimulate the ovary to produce prorenin but it is also possible that the ovary is indirectly involved, for example by stimulating the kidney to secrete more prorenin. We have measured the plasma levels of prorenin during two menstrual cycles in a woman who had undergone bilateral nephrectomy and was maintained on chronic haemodialysis.

Subject and methods

The woman was 34 years old and was nulliparous. She had had a bilateral nephrectomy 3 years previously because of end-stage renal failure resulting from vesico-ureteral reflux complicated by recurrent urinary infection Haemodialysis had been started a few weeks

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before nephrectomy. Her menarche had occurred when she was 13 years old and her menstrual cycle had been regular until the age of 25 years, when renal failure developed and she became oligomenorrhoeic. After haemodialysis was started she remained oligomenorrhoeic for some time, but during the 6 months before the study, menstrual bleeding occurred for 4–5 days approximately every 6 weeks. Her medication consisted of oral phosphate-binding agents and vitamins. She received haemodialysis twice a week, the plasma urea rising to 20–23 mmol/l before each haemodialysis session. The blood pressure was normal (120/80–130/80 mmHg before dialysis).

Blood samples were obtained during two menstrual cycles. There was an interval of approximately 6 weeks between the two studied cycles. During the first cycle only prorenin and renin levels were measured. During the second cycle, in which blood was collected before each haemodialysis session, oestradiol, progesterone, LH and FSH were also determined.

All blood was sampled between 0800 and 0830 hours while the subject was in recumbent position for 30 min before the start of the haemodialysis. At home she had eaten a light breakfast.

Blood for renin and prorenin measurements was collected into polystyrene tubes containing EDTA (0·2 ml disodium EDTA in 10 ml blood, final concentration 6·25 mM). The samples were centrifuged at room temperature at 3000 *g* for 10 min, and plasma was stored at −20°C. The plasma levels of prorenin and renin were measured by indirect radioimmunoassay (RIA). Angiotensin I was generated by incubating the plasma with an excess of sheep angiotensinogen under standardized conditions and this was then estimated by RIA (Derkx *et al.* 1983 and 1986). Plasma prorenin was measured after it had been converted into renin by the addition of immobilised trypsin to the plasma. Results were expressed as milli-units of a standard of purified renin from human kidney (Medical Research Council standard 68/356, National Institute for Biological Standards and Control, London, UK) per litre. The difference between the results before and after treatment of plasma with trypsin was taken to be a measure of prorenin concentration. The detection limit was 0·5 mU/l. Interassay variability was assessed by weekly measurements of naturally occurring active renin and prorenin in a normal plasma pool (stored at −20°C) during a 9-month period. The mean value of naturally occurring active renin was 27 mU/l (SD 3 mU/l) (36 assays), the coefficient of variation was 11%.

Oestradiol was measured using a commercially available RIA (Diagnostic Products Corporation, Los Angeles, CA, USA). Progesterone was measured as described before (Jong de *et al.* 1974), and LH and FSH by immunoradiometric assays (Medgenix, B-6220 Fleurus, Belgium).

Results

In a previous study of 59 normal women we found plasma prorenin levels between 62 and 357 mU/l (geometric mean 151 mU/l) on days 7–12 of the menstrual cycle. Plasma renin in these women ranged from 4·7 to 59 mU/l (geometric mean 15·4 mU/l). There was little or no change in plasma renin during the menstrual cycle (Sealey *et al* 1985b; Derkx *et al.* 1986).

In the nephrectomized woman prorenin levels were measured on days 5, 18, 32, 39 and 47 of the first cycle, which lasted 47 days. The levels on days 32 and 39 were higher (186 and 217 mU/l) than on days 5, 18 and 47 (46, 83 and 51 mU/l respectively). In the second cycle, which lasted 45 days (Fig. 1), prorenin ranged from 13 to 34 mU/l in the period from day 4 to day 21 but had risen on days 32 and 36 to 150 and 126 mU/l, respectively. Prorenin then returned to levels between 36 and 43 mU/l. Throughout both cycles studied the renin levels were below the detection limit.

LH varied from 5·7 to 12·9 IU/l from day 4 to day 18 of the second cycle. An increase was seen from day 21 onward and a peak level of 49 IU/l was detected on day 32. Levels returned to below 20 IU/l from day 35 to the end of the cycle In our laboratory LH levels in normal women ($n = 17$) in the follicular phase range from 1·3 to 7·9 IU/l, with a midcycle peak of 53·0 IU/l (range 36·2 to 69·8). FSH levels were between 1·6 and 4·2 IU/l. In normal women ($n = 10$) we have observed plasma levels of 1·2 to 4·2 IU/l in the follicular phase with a midcycle peak of 10·0 (range 7·9 to 12·1).

Oestradiol levels in the nephrectomized woman were approximately 500 pmol/l from day 4 to day 21, rose to a peak of 1105 pmol/l on day 32 and then returned to the initial level (normal women: 75–370 pmol/l in the early follicular phase, midcycle peak 740–1280 pmol/l, 220–730

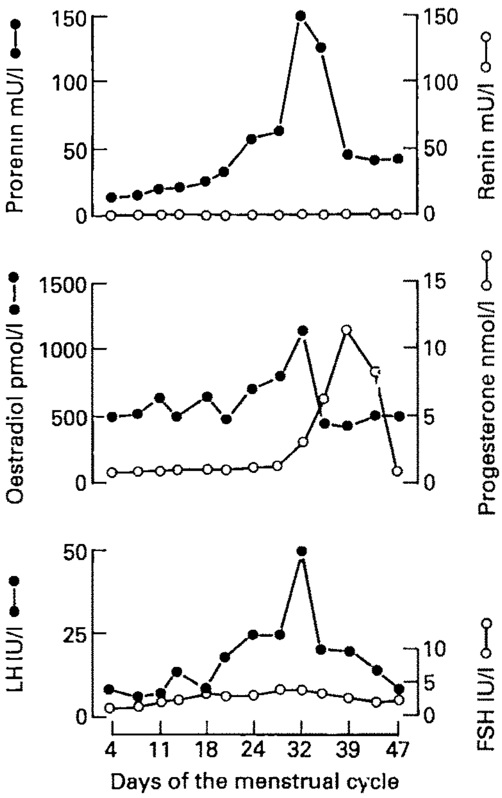

Fig. 1. Plasma levels of prorenin, renin, oestradiol, progesterone, LH and FSH during the second menstrual cycle in a nephrectomized patient

pmol/l in the luteal phase). Plasma progesterone in the nephrectomized woman ranged from 0·7 to 1·0 nmol/l in the first part of the cycle, showed a gradual increase to 11·1 nmol/l on day 39 and had returned to <1 nmol/l by day 47 (normal women: follicular phase: 0·6 to 3·2 nmol/l, start of luteal phase >3·2 nmol/l, mid luteal phase >30 nmol/l).

Discussion

The nephrectomized woman we studied showed fluctuations of plasma prorenin, LH, and oestradiol during the prolonged menstrual cycle that were similar to those in menstruating women with normal kidney function. FSH levels, albeit not showing a peak concomitant with the LH peak, were higher at midcycle, when compared with levels at the beginning and the end of the cycle. The absence of a detectable FSH peak may have been due to the fact that estimations were only performed twice weekly; the high level of LH is likely to be the descending limb of the midcycle gonadotrophin peak. In general, LH levels appear to be increased in uraemic women, whereas FSH levels are not different from those in normal women (Handelsman 1985). Finally, progesterone levels during the second half of the cycle were elevated but not enough to indicate normal luteal function, as has been described earlier (Morley *et al.* 1979).

Prorenin is the zymogen of renin, an aspartyl protease involved in the cascade of proteolytic enzymes that leads to the formation of angiotensin II, an octapeptide with important vascular actions. In plasma up to 90% of renin circulates in the form of prorenin and the kidney is an important source of plasma prorenin (Sealey *et al.* 1980; Derkx *et al.* 1983). In bilateral nephrectomized patients renin is very low or below the detection limit whereas prorenin is about 30% of normal (Derkx & Schalekamp 1988). Some anephrics have prorenin levels within the normal range. Possible extrarenal sources for prorenin are the adrenals (Lenz & Sealey 1990), testis (Sealey *et al.* 1988), uterus (Warren *et al.* 1982) and the eye (Deinum *et al.* 1990). Prorenin but not renin is higher in men than in women (Plouin *et al.* 1989).

The rat ovary expresses renin (Kim *et al.* 1987) and gonadotrophin regulated secretion of prorenin occurs during normal ovulation (Sealey *et al.* 1985b; Derkx *et al.* 1987) without concurrent changes in plasma renin.

As in normal women, the prorenin peak in our subject appeared close to the time of the LH peak and preceded the rise of progesterone but, in contrast to women with intact kidneys, renin was below the detection limit throughout the cycle. These results demonstrate that the changes in prorenin that occur during the menstrual cycle in normal women do not depend on the presence of the kidneys. They are in keeping with the hypothesis that the ovary is a source of prorenin in plasma and that LH and/or FSH may stimulate the secretion of prorenin by the ovary. The absolute rise in plasma prorenin during the menstrual cycle in our subject was of the same magnitude as that seen in normal women (Sealey *et al.* 1985b). This is an indication not only that the kidneys are not essential in this respect but also that they do not contribute in a major way to the changes in plasma prorenin that occur in the normal menstrual cycle. A high concentration of prorenin has been found in ovarian follicular fluid shortly before ovulation in women with hyperstimulated cycles (Glorioso *et al.* 1986;

Derkx *et al* 1987). Prorenin in plasma at that time is about twice that observed early in the follicular phase. The increase in plasma prorenin during both normal and hyperstimulated menstrual cycles seem to reflect increased ovarian production of prorenin.

Not only prorenin but also renin substrate, angiotension converting enzyme (Derkx *et al.* 1987) and immunoreactive angiotension II have been found in high concentrations in human ovarian follicular fluid (Culler *et al.* 1986). In the woman the theca cells seem to be the source of the large quantities of prorenin in ovarian follicular fluid (Do *et al.* 1988). Prorenin may have intrinsic catalytic activity (Heinrikson *et al.* 1989) and may initiate the cascade of events leading to the formation of angiotensin II Furthermore angiotensin II receptor binding sites have been found in the ovary (Husain *et al.* 1987). Thus there is increasing evidence for a local renin-angiotensin system in the ovary and this may serve as autocrine or paracrine regulator of ovarian function. Recently it has been reported that saralasin, a specific receptor antagonist of angiotensin II, the active end-product of the renin-angiotensin cascade, can block ovulation in the rat (Pellicer *et al.* 1988), indicating a direct role for the renin-angiotensin system in the regulation of ovulation.

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Transvaginal ultrasound for diagnosis of uterine malformations

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Summary. Uterine malformations were detected in 8 of 300 patients (3%) referred for transvaginal ultrasound scan (TVS) for different indications. Six of them had a partially septate uterus and two had a uterus didelphys. As uterine malformations can be associated with both sterility and reproductive failure, we suggest that the study of uterine morphology and structure could be a part of routine TVS examination.

Congenital malformations of the uterus caused by mullerian duct fusion defects include uterus didelphys, bicornuate uterus and septate uterus. Only 25% of patients with these conditions have reproductive problems, mostly associated with uterine septa, which cause a high rate of pregnancy loss (Buttram *et al.* 1979, Jones 1981). Because many of these malformations are clinically silent, their true prevalence is difficult to ascertain but it has been reported to be between 0.1% and 1% (DeCherney 1984). There is an increase in urological anomalies associated with uterine malformations. Mercer *et al.* (1981) reported a figure as high as 20% for the associated occurrence of renal anomalies. As a general rule, the more severe the uterine malformation, the greater is the likelihood of a coexisting urological anomaly. The aim of this study was to assess the frequency of uterine anomalies in a group of gynaecological patients with the use of transvaginal ultrasound scanning (TVS).

Patients and methods

The study included 300 women who were referred to the ultrasound scan unit in the gynaecology department at St Bartholomew's Hospital for TVS. The indications for scanning are shown in Table 1.

The scan was performed with the patient supine and with the bladder empty. The probe was covered with a sterile lubricated condom and inserted into the mid-vagina. Images of the uterine body, fundus, and the cervix were obtained in the antero-posterior and transverse planes. The following data were recorded: (i) the external shape of the uterus; (ii) the presence and grade of the endometrial layer; (iii) the presence of a median endo-uterine septum at any point along its longitudinal axis. The adnexal areas and the posterior cul-de-sac were also identified.

Ultrasound examinations were performed using an ALOKA SSD-620 machine, with a 5 MHz vaginal probe giving a 60° angle view. Each examination took 5 to 10 min.

Results

A partial uterine septum was found in six women (2%) (Fig. 1). The uterine cavity was clearly seen in all six, especially in the four patients with thick endometrium characteristic of the luteal phase of the menstrual cycle (Nicolini *et al.* 1987). There was an increase in the transverse diameter of the uterus in five of the six women with partial septa; the external uterine morphology was normal in four and difficult to assess in two.

In two patients a complete uterus didelphys

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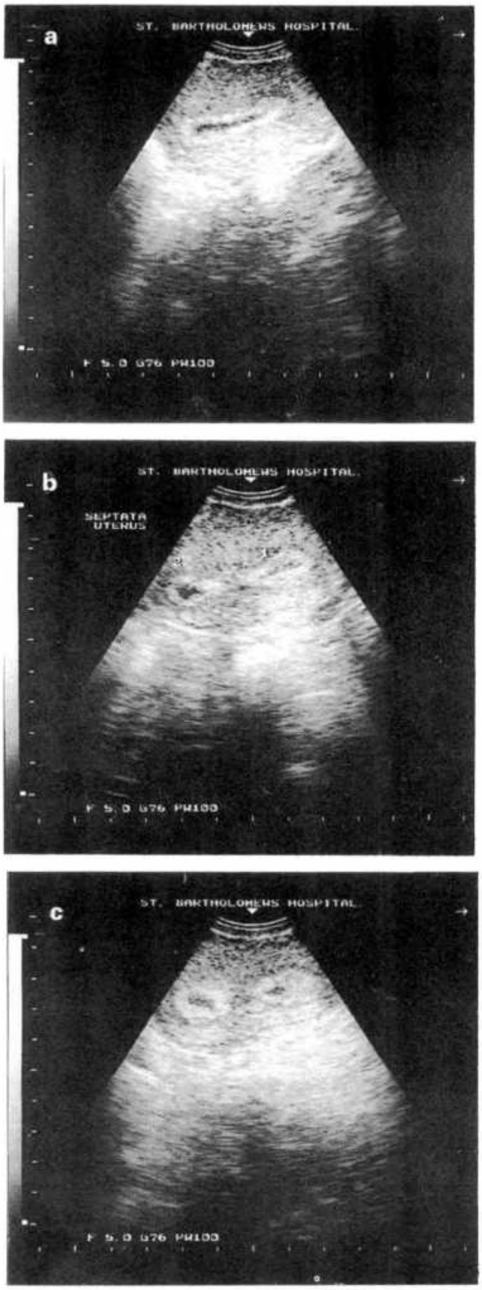
a
ST. BARTHOLOMEWS HOSPITAL
F 5.0 G76 PW100
b
ST. BARTHOLOMEWS HOSPITAL
SEPTATA UTERUS
F 5.0 G76 PW100
c
ST. BARTHOLOMEWS HOSPITAL
F 5.0 G76 PW100

Fig. 1. Transvaginal ultrasound scan showing serial transverse sections of the uterus indicating a septate uterus, between 1 and 2. (a) close to the cervix, (b) mid-cavity, and (c) close to fundus.

was diagnosed (Fig. 2). One was a 33-year-old woman with menorrahgia in whom hysterosalpingography (HSG) confirmed the diagnosis and intravenous urography showed no functioning left kidney, with compensatory hypertrophy of the right kidney. The other was an 18-year-old girl with pelvic pain in whom urography showed a large left kidney and no right kidney (HSG was not done). Table 2 summarizes the clinical details of the eight patients with uterine malformations.

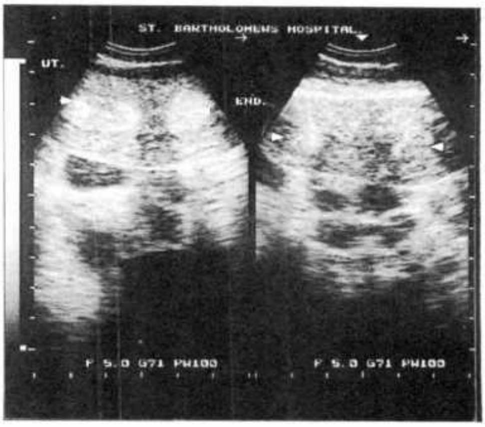

Fig. 2. Transvaginal ultrasound scan of a transverse section of the uterus (double image) showing two endometrial hemicavities (arrowheads) with a septum between the inner margins (didelphic uterus).

Discussion

This is the first study in which TVS has been used to detect uterine malformations in a largely unselected group of gynaecological patients. Previous ultrasound studies focused mainly on congenital abnormalities of the uterus during pregnancy and the puerperium (Jones *et al.* 1980), with isolated reports on nonpregnant patients (Valdes *et al.* 1984).

Although physical examination may reveal an obvious malformation, more often the diagnosis is made in the course of curettage, hysterosalpingography, hysteroscopy or laparoscopy. This

Table 1. Indications for transvaginal ultrasound

Indication	Number
Pelvic pain	70
Abnormal uterine bleeding	64
Pelvic mass	56
Pregnancy complications	46
Infertility and cycle tracking	21
Dysmenorrhea	18
Dyspareunia	10
Lost intrauterine device	8
Endometriosis	7
Total	300

Table 2. Clinical details of eight women with uterine malformations detected at transvaginal ultrasound scanning (TVS)

No.	Presenting symptom	Age (years)	Parity	TVS findings
1.	Menorrahgia	33	P0+1	Uterus didelphys
2.	Pelvic pain	18	P0+0	Uterus didelphys
3	Dyspareunia	23	P1+0	Septate uterus
4	Late period	29	P2+1	Septate uterus
5	Intermenstrual bleeding	34	P0+0	Septate uterus
6	Pelvic mass	19	P0+0	Septate uterus
7.	Pelvic pain	25	P0+0	Septate uterus
8.	Infertility and hirsutism	26	P0+0	Septate uterus

study suggests that the prevalence of uterine malformations may be higher than previously reported. The most common abnormality identified was the partially septate uterus, which is one of the leading anatomical causes of repeated first-trimester pregnancy loss (Rock *et al.* 1985). Patients with a malformed uterus may benefit from an open or hysteroscopic metroplasty operation (Capraro *et al.* 1968, DeCherney 1983).

Transvaginal ultrasound scanning may replace HSG as an initial screening test for uterine malformations, to be followed by more invasive procedures, such as hysteroscopy, laparoscopy, or HSG only in the small number of patients with ultrasonically demonstrated abnormalities.

A useful additional outcome of screening for uterine abnormalities is the detection of coexisting urological anomalies (Morgan *et al.* 1987). It is of potential benefit for a woman to be aware that she has asymptomatic unilateral renal agenesis, as this information could be life saving in certain circumstances. Whenever possible, TVS should be recorded in the luteal phase of the menstrual cycle, because the endometrium is then thicker and abnormalities can be more clearly identified. TVS is a safe, comparatively noninvasive procedure which can be used to screen for morphological abnormalities of the uterus in the general population, as well as in patients with a history of recurrent pregnancy loss. The study of uterine shape and dimensions could become a routine part of gynaecological ultrasound examination.

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Small cell undifferentiated carcinoma of the cervix. Case report

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Case report

A 27-year-old woman, para 2, was referred to the gynaecology clinic with a clinically suspicious cervix. She reported an offensive brown vaginal discharge and low back pain but denied menstrual irregularity. During the preceding week she had also developed nausea and intermittent diarrhoea and constipation. She had been seen in our department twice in the previous year: initially for laparoscopic sterilization and subsequently (5 months before the current attendance) with menorrhagia and a vaginal discharge, when she was noted to have a chronically infected cervix. Cervical cytology was negative and her symptoms resolved after treatment with systemic antibiotics and povidone-iodine pessaries.

The appearance on vaginal examination was consistent with cervical carcinoma but a cervical smear was negative and histology of a punch biopsy showed only necrotic tissue. She was admitted to hospital and over the following 48 h she became pyrexial and developed a cough, dyspnoea and left side chest pain. Examination revealed pyrexia (38·6°C), tachycardia (96 beats/min) and decreased resonance and breath sounds over the base of the left lung. Chest X-ray confirmed a left pleural effusion. Her haemoglobin concentration was 10·3 g/dl, leucocyte count 19·8 × 10^9/l, and ESR 100 mm/h. Alkaline phosphatase was raised at 294 IU/l, as was her GGT at 96 IU/l. Cultures of blood, urine, sputum and vaginal discharge were negative. Ultrasound examination revealed a large irregular mass in the region of the cervix, an obstructed left kidney, and a mass in the tail of the pancreas. The pleural effusion was drained, cytology and culture of the aspirate were negative.

At examination under anaesthesia the cervix was found to be completely replaced by a 7 cm diameter, firm, white mass. The tumour was fixed to the pelvic side wall on both sides. The mass indented but did not invade the rectum. The lower two thirds of vagina were free of tumour, but a 4 cm diameter mass was easily palpable in the epigastrium. Cystoscopy showed the left side of the bladder to be indented but there was no evidence of tumour invasion. A wedge biopsy of the cervix was taken.

Microscopy showed poorly differentiated carcinoma infiltrating beneath normal cervical epithelium (Fig. 1). The tumour cells varied in size, but were mostly small with scanty basophilic cytoplasm. Nucleoli were infrequent but there was a high mitotic rate. In places the nuclei exhibited ‘smearing’ artefact similar to the appearances seen in oat cell carcinoma of the bronchus. There was extensive necrosis but no evidence of squamous or glandular differentiation. The Grimelius silver stain was negative. Immunohistochemistry revealed strong positivity within some of the tumour cells for chromogranin and S-100, and weak positivity for neurone specific enolase. Electron microscopy showed membrane-bound intracytoplasmic granules, compatible with neuro-endocrine granules, in some tumour cells. A diagnosis of small cell undifferentiated carcinoma of the cervix was made, with immunohistochemical and ultrastructural evidence of neuro-endocrine differentiation.

This was an extensive cervical tumour with clinical evidence of para-aortic or pancreatic and lung metastasis. It was clinically a stage IVb car-

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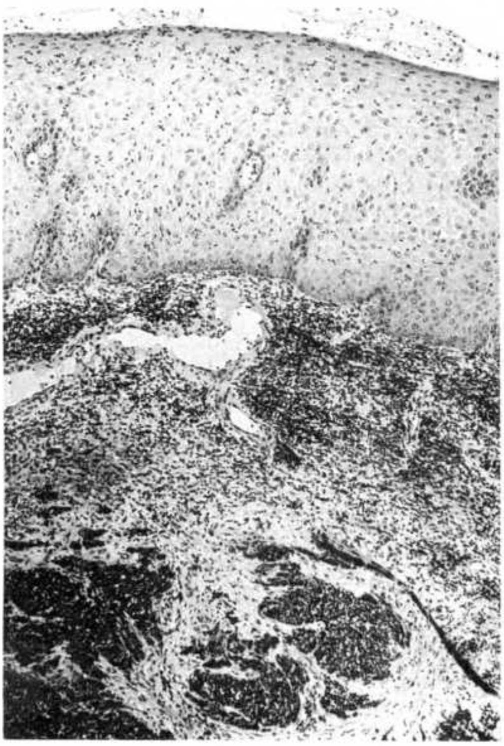

Fig. 1. Photomicrograph of the cervical biopsy shows tumour infiltrating beneath the normal ectocervical epithelium.

cinoma of cervix. The patient was treated with a regimen of cisplatin, 65 mg, and bleomycin, 13 mg, given intravenously over 4 h and 1·8 mg of vincristine. Chemotherapy was discontinued due to the patient's rapidly deteriorating condition. She developed pneumonia and died 9 weeks after presentation and 5 weeks after chemotherapy.

Discussion

Small cell undifferentiated carcinoma is a rare cervical tumour which is being increasingly recognized (MacKay *et al.* 1979; Groben *et al.* 1985; Gersell *et al.* 1988). It is at the poorly differentiated end of the spectrum of those cervical tumours which show evidence of neuro-endocrine differentiation. As with all neuro-endocrine tumours of the cervix, this tumour tends to produce a large, bulky, vegitating mass which encompasses and destroys the entire cervix. In our patient the tumour was 7 cm in diameter which is larger than any reported previously. It is interesting that cervical cytology failed to show malignant cells. The small cell undifferentiated carcinoma appears to be a highly aggressive neoplasm, and there is recent evidence to suggest that even the better differentiated neuro-endocrine tumours, cervical 'carcinoids', which were previously regarded as being low grade, can be equally aggressive (Groben *et al.* 1985). The tendency is to metastasize early and disseminate widely, therefore careful staging is required to assess thoroughly the extent of the disease before initiating treatment. Both radical surgery and combinations of radiotherapy and chemotherapy have been used in the treatment of small cell undifferentiated carcinomas, with equally poor results. Temporary remissions have been achieved, but early recurrence is likely and most patients die from the disease within a year of diagnosis (Gersell *et al.* 1988).

As is often the case the disease was already widespread when chemotherapy was started. However, the patient's condition deteriorated remarkably quickly, demonstrating the very aggressive nature of this type of carcinoma. This is true even if the cervical appearance at her previous clinic attendance was due to early malignancy rather than chronic infection, which must be considered a possibility.

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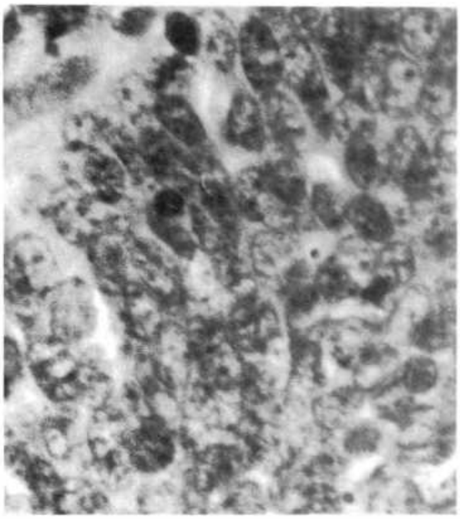

Fig. 2. Higher power of photomicrograph shows the tumour is composed of compact cells with scanty cytoplasm.

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Hypercalcaemia in pregnancy in a renal transplant recipient with secondary hyperparathyroidism. Case report

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Case report

A 28-year-old woman was seen in her first pregnancy in 1984. At 23 years of age she received a renal transplant from her HLA identical brother. During the 30 months before the transplant she was maintained on haemodialysis because of end-stage renal disease secondary to chronic glomerulonephritis dating from 9 years of age. Since transplantation she had taken azathioprine 50 mg daily and prednisone 10 mg daily. Blood pressure and renal function were normal. After 3·5 years from transplantation, mild hypercalcaemia and increased levels of serum parathyroid hormone (PTH) were found. A low calcium diet and bisodium phosphate in doses equivalent to 2·2 g/day of phosphorus were added to her existing treatment, and she had a satisfactory clinical and humoral course during the following 15 months.

At her first visit after conception (at 9 weeks gestation) her serum calcium was raised (Fig. 1). The clinical course was satisfactory up to 25 weeks gestation, at which time her blood pressure began to increase (140/85 mm Hg) compared with her first trimester normal values. The levels of ionic serum calcium and serum 1,25-dihydroxy vitamin D (1,25$(OH)_2$D) also increased compared with normal values.

At 28 weeks gestation she was admitted to hospital because her blood pressure was 145/95 mm Hg. Hydralazine (200 mg/24 h) and 1α-methyldopa (1 g/24 h) were added to her treatment.

At 30 weeks gestation, total serum calcium had increased to 3·65 mmol/l from previous levels of 2·93 mmol/l. Bisodium phosphate was discontinued and an intravenous infusion of 2000 ml per day (2/3 glucose 5%; 1/3 NaCl 0·9%) with salmon calcitonin (100 units every 4 h) were given. The dose of salmon calcitonin was increased slowly during the next 18 days up to 2400 units per day and the serum calcium diminished to 2·68–2·72 mmol/l (Fig. 1).

At 33 weeks gestation the creatinine clearance decreased (82·1 ml/min), proteinuria appeared (1 g/24 h), and the diastolic blood pressure was persistently at 100 mm Hg. The pregnancy was terminated by caesarean section and a 1600 g female baby was born. Clinical and neurological examination of the baby were normal, and mother and child had an uneventful immediate post-partum course.

At 19 weeks after delivery, total and ionic serum calcium, urinary calcium and 1,25$(OH)_2$D levels were in the normal range, but serum PTH values had increased to 310 pg/ml.

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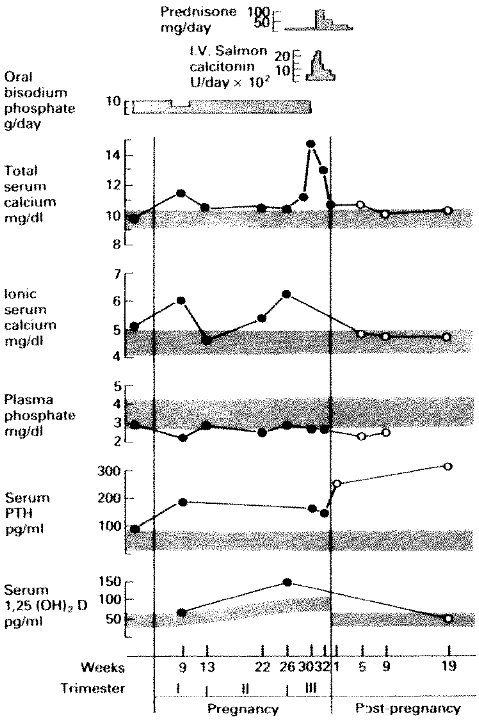


Fig. 1. Marked hypercalcaemia associated with a decrease of serum parathyroid hormone (PTH) in the third trimester of pregnancy. Conversion factors to SI units. Serum calcium: mmol/l×4 = mg/dl; plasma phosphate mmol/l × 3·1 = mg/dl.

Investigations

Serum and urinary calcium were determined by atomic absorption spectrophotometry and ionic serum calcium was determined with an ion-selective electrode (normal values: 1·02–1·21 mmol/l). Plasma phosphorus and creatinine were measured by standard methods.

Serum PTH was determined by radioimmunoassay using an antiserum that recognises the mid and carboxy terminal fragment of the PTH molecule. As tracer and standard the fragment 43–68 of the molecule was used (normal values: 20–90 pg/ml). Serum 1,25$(OH)_2D$ was measured using the method described by Shepard *et al.* (1979); the normal values are between 30 and 60 pg/ml; at the end of the first trimester of pregnancy the upper limit increases normally to 80 pg/ml and during the third trimester the normal range is between 60 and 100 pg/ml.

The placenta was studied by light microscopy as described previously (Labarrere *et al.* 1985). The histological sections were studied with haematoxylin and eosin, Periodic-Acid-Schiff (PAS) and Masson's trichrome. Immunohistochemical studies for 1,25$(OH)_2D3$ were performed in 5 μm sections from the placenta in ten paraffin embedded blocks using an immunoperoxidase procedure described previously (Labarrere *et al.* 1985). Sections were incubated with rabbit antihuman antibody to 1,25$(OH)_2D3$ (Hummer *et al.* 1985) at a 1:1000 dilution. Swine antirabbit IgG (1:50) was used as second antibody, and rabbit PAP complexes (1:50) (both from Dakopatts, Denmark) were subsequently used. The immune reaction was developed with diaminobenzidine (Sigma) and hydrogen peroxide. All antisera were diluted in phosphate buffer saline (PBS, pH 7.4) which was also used for washes between incubation steps. To enhance immunoreactivity which may be lost by formalin fixation, sections were submitted to trypsin digestion as described previously (Labarrere *et al.* 1985). The following controls were used to check the validity of the procedure: (i) omission of the primary antiserum; (ii) use of non-immune rabbit serum as primary antibody; (iii) preabsorption of the primary antibody with its respective antigen (1,25$(OH)_2D3$).

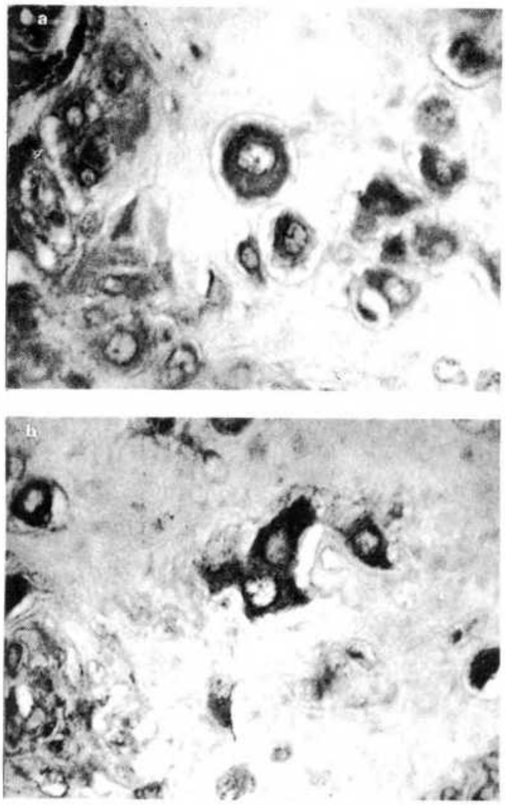
Ten placentas of similar gestational age, from women free of any disease before, during or after pregnancy served as controls. All these placentas had villous maturation similar to that in our patient and no evidence of infection.

Placental findings

The placenta weighed 245 g and measured 15×12×2 cm. Histologically the villi were normal in appearance, but showed a high proportion of fibrinoid necrosis. The placenta also had areas of anchoring villitis (Labarrere & Althabe 1985) in the basal plate.

The immunostaining with 1,25$(OH)_2D3$ antibody showed a dark brown cytoplasmatic reactivity in most of the cytotrophoblastic cells in the septa and in the basal plate (interstitial cytotrophoblast) (Faulk and McIntyre 1983) (Figs. 2a and b).

No immunoactivity was observed in interstitial cytotrophoblastic cells of the normal placentas used as controls. A weak reactivity was observed in stromal cells and syncytiotrophoblast of some villi in controls as well as in the studied case (data not shown). The immunoreactivity was uniformly negative in all the con-



Figs. 2a and b. A dark cytoplasmatic reactivity is seen in most of the cytotrophoblastic cells in a septa (interstitial cytotrophoblast). No nuclear reactivity is found in any cell. 1,25(OH)$_2$D3 antibody was used as primary antiserum. Immunoperoxidase stain, haematoxylin counterstain (×400).

trol procedures, including the use of absorbed antiserum.

Discussion

Since Murray *et al.* (1963) reported the first observation of a patient with a renal transplant who had two successful pregnancies, many other similar cases have been published. Hou (1985) in a review article mentioned 1200 cases.

Persistent hypercalcaemia due to secondary hyperparathyroidism after kidney transplantation is a frequent observation (Cundy *et al.* 1983). We found only one report (Delmonico *et al.* 1976) in which a patient with a renal transplant underwent a subtotal parathyroidectomy due to severe hypercalcaemia in the second trimester of pregnancy. It was predicted that this would be a more frequent occurrence as the number of successful renal transplants in women increases.

In the present report an increase of total and ionic serum calcium and serum 1,25(OH)$_2$D was observed at the beginning of the third trimester of pregnancy associated with serum PTH levels below those observed in the first part of gestation (Fig. 1). After delivery, total and ionic serum calcium and 1,25(OH)$_2$D levels decreased to normal and serum PTH increased. The disturbance in circulating levels of total and ionic serum calcium and 1,25(OH)$_2$D observed in our patient may reflect placental rather than renal function. Indeed, 1,25(OH)$_2$D (Weisman *et al.* 1978) and 1,25(OH)$_2$D3 (Gray *et al.* 1979) have been found in plasma of nephrectomized pregnant rats.

In normal human pregnancy an increase in circulating 1,25(OH)$_2$D has been observed after 6 weeks gestation (Reddy *et al.* 1983) and this reaches a plateau at the end of the first trimester (Reddy *et al.* 1983; Gertner *et al.* 1986). Cushard *et al.* (1972) found an increase in serum PTH during the third trimester of human pregnancy, but the most recent studies have not confirmed this. Several authors have found decreased levels of serum PTH during pregnancy (Reddy *et al.* 1983; Gertner *et al.* 1986; Davis *et al.* 1988). The opposite changes in serum 1,25(OH)$_2$D and serum PTH may be explained by the presence of cytoplasmic and nuclear receptors for 1,25(OH)$_2$D in parathyroid glands (Wesckler *et al.* 1977), and by the decrease in serum PTH due to the increased serum 1,25(OH)$_2$D. This effect has been observed in rats (Au 1984) as well as in the human (Slatopolsky *et al.* 1984; Breslau & Zerwekh 1986).

Although high levels of PTH were found during and after pregnancy, this rise was associated with calcium levels near the upper limits or in the normal range. A relative decrease in serum PTH was associated with the marked hypercalcaemia observed in the third trimester. Although 1,25(OH)$_2$D was not measured at the time of the hypercalcaemia, high levels were detected during the third trimester. The normal values for 1,25(OH)$_2$D found after delivery, the return to normocalcaemia and the increase in serum PTH suggest a placental origin for the 1,25(OH)$_2$D.

Turner *et al.* (1988) reported a patient with end-stage renal disease and severe secondary hyperparathyroidism who conceived after 10 years of chronic haemodialysis and gave birth to a preterm baby at 25 weeks gestation. Interestingly, increasing serum calcium concentrations were noted after 22 weeks gestation, despite discontinuation of previous oral calcium supplementation treatment, and oral $1,25(OH)_2D_3$ therapy was then discontinued. Following delivery, the patient's serum calcium concentration fell and oral calcium and $1,25(OH)_2D_3$ treatment had to be resumed. Although her serum $1,25(OH)_2D$ concentrations without exogenous supplementation did not increase significantly after 23 and 24 weeks gestation, they were almost twice her own basal values. Since the patient was delivered at 25 weeks gestation, the possibility of a further increase in the concentrations of serum calcium and $1,25(OH)_2D$ later during the third trimester, as was found in our patient, cannot be excluded.

Many authors (Weisman *et al.* 1979; Whitsett *et al.* 1981; Delvin *et al.* 1985; Zerwekh & Breslau 1986) reported the production of $1,25(OH)_2D$ by human placental tissue in vitro. Weisman *et al.* (1979) reported the production of $1,25(OH)_2D$ by the placental decidua and Zerwekh & Breslau (1986) observed the presence of 25-OH-D_3-1α-hydroxylase in the mitochondria of fetal trophoblastic cells. No reports have been published using immunohistochemical techniques to locate the precise site of $1,25(OH)_2D$ in the placenta. The recognition of the placental cytotrophoblastic cells in the basal plate and septa (interstitial cytotrophoblast) in our patient as the probable site of synthesis of $1,25(OH)_2D3$ is a contribution to the study of this problem.

Acknowledgments

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Endocrinological aspects of a Sertoli-Leydig cell tumour. Case report

T. VAN DESSEL, M. J. HEINEMAN

Case report

A 29-year-old woman was admitted to hospital one week after her first delivery because of low-grade pyrexia. The admission diagnosis was sub-involutio uteri. She had been treated with antibiotics and ergometrine by the family physician but her condition had not improved.

Antenatal care had been provided by a midwife. At about 31 weeks gestation, the patient noticed development of hirsutism. At about the same time her voice deepened, and her clitoris became painfully enlarged. Relatives and family noticed a 'masculine look'.

At 35 weeks gestation she had an ultrasound at another hospital for suspected macrosomia. No abnormalities were reported.

The patient was delivered uneventfully at term at home, assisted by her midwife. A healthy girl was born with a birthweight of 3500 g and Apgar scores of 7, 8 and 10 at 1, 5 and 10 min. The placenta appeared macroscopically normal. The baby showed no signs of virilization and the neonatal course was uneventful.

On admission to our hospital, 8 days post partum, the patient had a temperature of 38·5°C. The abdomen was distended (abdominal circumference: 90 cm). A large tumour, extending to halfway between the umbilicus and the xiphoid process could be palpated but the uterus appeared to be normal.

There were no signs of endometritis. The clitoris was markedly enlarged (3 × 2 × 2 cm) and painful. The patient's voice was low and hoarse. Moderate hirsutism was present; there was hair growth on upper lip, chin and legs.

Investigations

The endocrinological variables investigated are shown in Fig 1. Steriods were estimated with a solid phase ^{125}I radioimmunoassay. Reference values: oestradiol, 0·11–0·18 nmol/l (early follicular); testosterone, 0·5–3·0 nmol/l; progesterone, 0·3–0·5 nmol/l (early follicular) and 8–90 nmol/l (luteal). Follicle stimulating hormone (FSH) and luteinizing hormone (LH) were measured using a double-antibody ^{125}I radioimmunoassay. Human chorionic gonadotrophin (hCG) was measured by the Nijmegen-hCG test

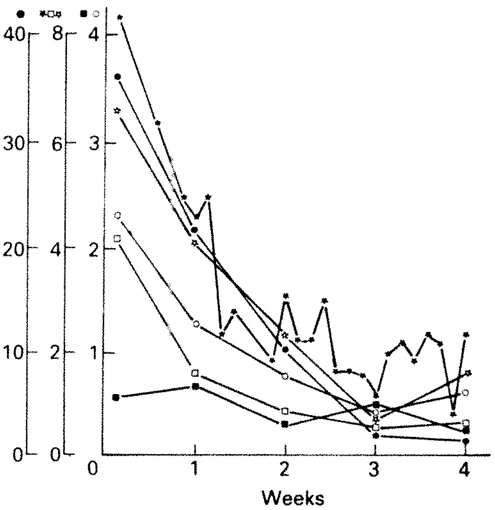

Fig. 1. Serum hormone concentrations in the first 4 weeks after presentation at 8 days postpartum, ★, β-human chorionic gonadotrophin (ng/ml); ☆, progesterone (nmol/l); ●, testosterone (nmol/l); ○, oestradiol (nmol/l); □, luteinizing hormone (iu/l); ■, follicle stimulating hormone (iu/l).

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(Thomas 1985) (conversion factor for β-hCG: log[hCG (ng/ml)] = 0·8362 × log[1st IRP-hCG (IU/l)]–0·9827. The relative cross reaction with the LH-assay is 0·100 for hCG, the cross-reactivity with the hCG-assay is 0·037 for LH. The most striking finding was an elevated testosterone level (37 nmol/l).

Ultrasound examination revealed a multiple cystic mass extending throughout the entire abdomen (30 × 25 × 20 cm). Multiple echo-free cysts ranging from 3 to 12 cm in diameter were seen. The intercystic septae were thin. Only a few solid parts were found, mainly in the interseptic lining. No normal ovarian structures could be identified either in the left or right ovary. The uterus was normal for the 8th day post-partum. Computer tomography studies confirmed the ultrasound findings. Again no normal ovarian structures could be found. The cystic mass appeared to be a bilateral ovarian process. During the entire treatment of this patient the left ovary was never positively identified as normal.

A transabdominal, ultrasound guided puncture of the tumour was performed. There were no malignant cells in the collected tissue and fluid. A histopathologic diagnosis could not be made.

Serum levels of β-hCG decreased in the first weeks after admission but remained detectable. Dilatation and curettage provided no histological evidence of hydatidiform mole, chorioncarcinoma or placental remnants.

Daily measurement of the abdominal circumference showed a decline from 90 to 70 cm within one month. The ultrasound appearance of the tumour changed, the large number of cysts decreased to approximately 20 and they became smaller. One 'reference' cyst was measured twice a week and showed a decline from 9 to 3·5 cm. The tumour size declined to 24 × 20 × 16 cm. Body temperature became normal within 3 weeks.

A provisional diagnosis of 'hyperreactio luteinalis' was made, based on the large cystic mass, the virilization, the endocrinological findings and the coincidence with pregnancy.

To prove the bilateral ovarian origin of androgen production, ovarian and adrenal venous blood samples were taken using the Seldinger technique. Blood was collected from both adrenal veins and the left ovarian vein but the right

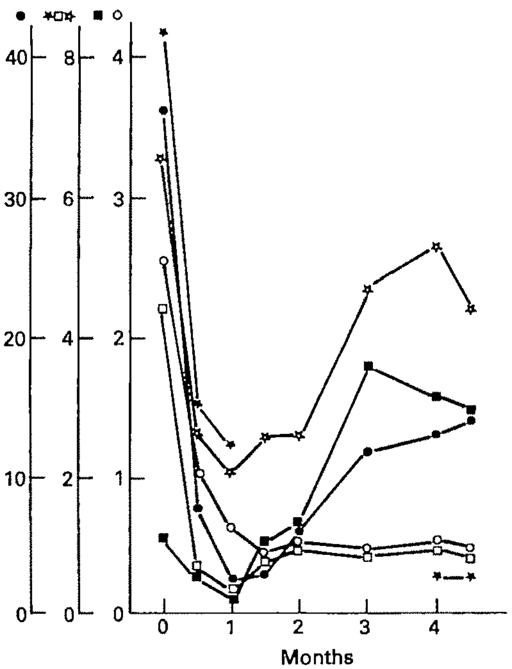

Fig. 2. Serum hormone concentrations during the first 5 months after presentation (phase 1, no treatment). For explanation of symbols see Fig 1

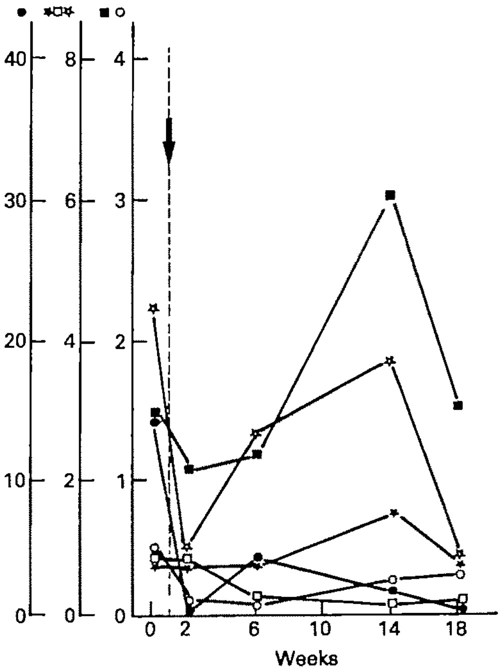

Fig. 3. Serum hormone concentrations during treatment with a low dose oral contraceptive The arrow indicates the start of therapy For explanation of symbols see Fig 1

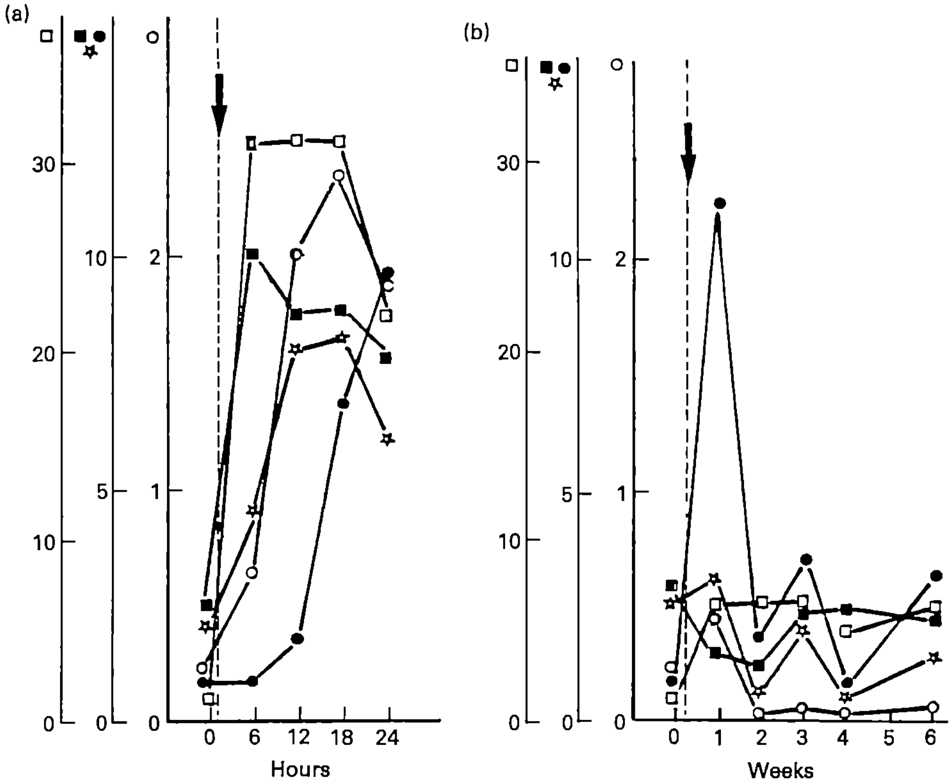

Fig. 4. Serum hormone concentrations during treatment with buserelin (a) the first 24 h, (b) the next 6 weeks. The arrow indicates the start of therapy. For explanation of symbols see Fig. 1.

ovarian vein could not be sampled for technical reasons. It was demonstrated that at least the ovary was the source of excessive androgen production (testosterone in left ovarian vein: 44 nmol/l, in adrenal veins 2·1 and 3·5 nmol/ml).

Treatment and outcome

Our provisional diagnosis of 'hyperreactio luteinalis' and the patient's refusal of surgical treatment led us to use conservative treatment. The treatment adopted can be divided into four phases. During phase 1, the patient received no medication and the spontaneous regression of the tumour was monitored for 5 months. After that, during phase 2, the patient was treated with a combined low oestrogen oral contraceptive (0·03 mg ethinyl oestradiol plus 150 mg levonorgestrol) for 5 months (21 user days each month). In phase 3 she was treated with the LHRH—analogue, buserelin (Hoechst AG). This was given subcutaneously (300 μg twice daily) for 2 weeks, followed by intranasal administration (300 μg four times daily) for 6 weeks. Finally a laparotomy and ovariectomy was performed (phase 4). Follow-up 1 year after surgery showed the patient to be without signs of recurrent disease. Her periods were regular and her hormonal status was completely normal.

Phase 1, (Fig. 2)

During the 5 months of phase 1 without medication our patient did not have any periods. An attempt to breast-feed was not successful because of insufficient lactation. The virilization features gradually diminished. Within one month the clitoris became smaller but slight hirsutism remained. Her voice changes were permanent.

In the first month after admission, declining serum levels of β-hCG, LH, FSH, oestradiol, testosterone and progesterone were found. The intial drop in testosterone levels was followed by a gradual rise, β-hCG fell to undetectable levels and FSH as well as progesterone concentrations increased. Only in the first month was there a substantial reduction in size of the intra-abdominal masses. Ultrasound showed a reduction in the number of cysts and the tumour seemed to

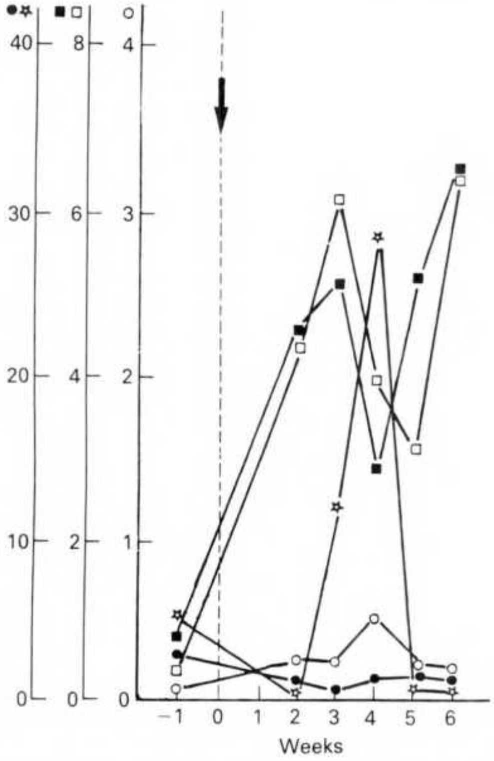

Fig. 5. Serum hormone concentrations before and after ovariectomy. For explanation of symbols see Fig. 1.

consolidate. A recommended laparotomy was refused by the patient.

Our hypothesis was that the initial improvement did not continue because of persisting ovarian stimulation. Since oral contraceptive therapy has been shown to assist the resolution of functional ovarian cysts, a low oestrogen dose oral contraceptive was prescribed.

Phase 2 (Fig. 3)

Immediately after the start of the treatment with an oral contraceptive a sharp decline in testosterone, oestradiol and progesterone levels was seen. Later FSH and progesterone levels rose again. As became apparent later, the patient's compliance was not optimal. The intra-abdominal masses showed no substantial reduction in size or change in appearance during the 5 months of treatment.

Phase 3 (Fig. 4)

After almost 1 year of conservative therapy, surgical treatment was unavoidable. We believed that a reduction in tumour size would facilitate the operation and increase the possibility of preserving some functional ovarian tissue. A LHRH-analogue (buserelin) was administered to achieve a hypogonadotrophic state and consequently more tumour size reduction.

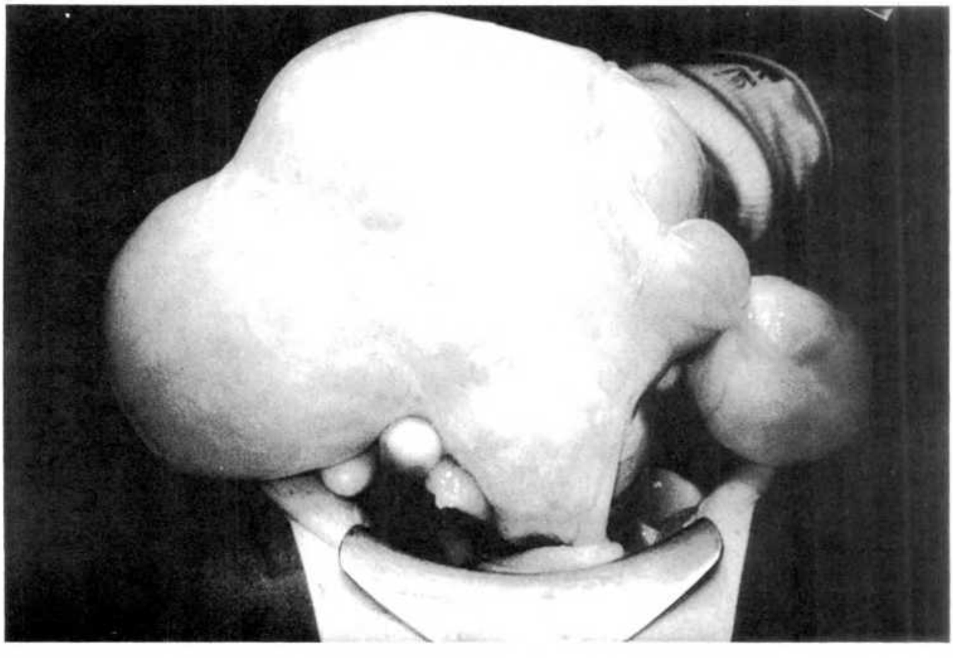

Fig. 6. Findings during surgery: large tumour of the left ovary.

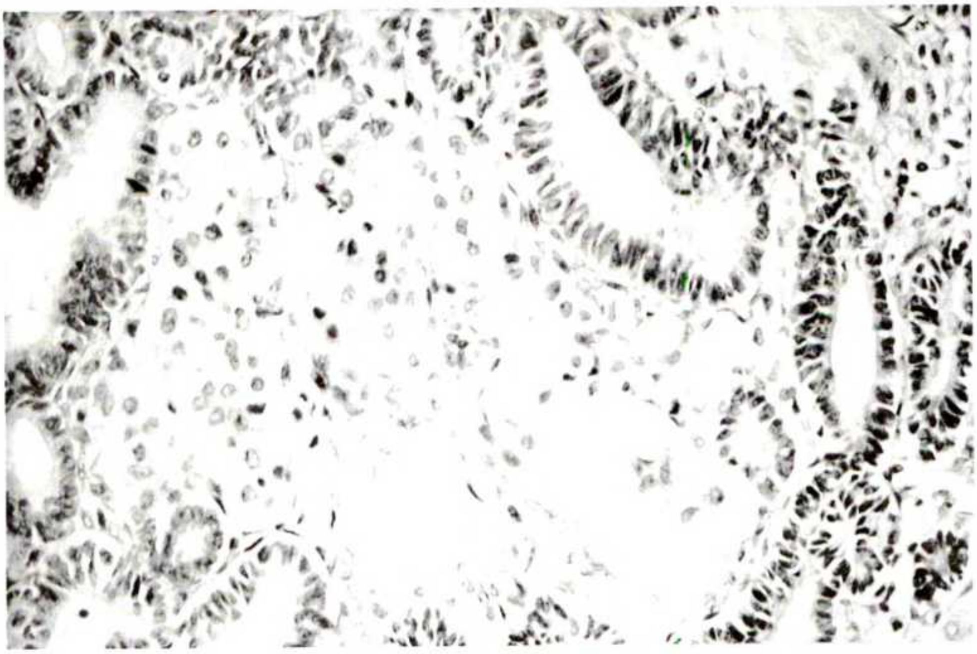

Fig. 7. Well differentiated Sertoli-Leydig cell tumour.

In the first 24 h of buserelin administration the levels of LH, FSH, oestradiol, testosterone and progesterone rose remarkably (Fig. 4a). Low levels were reached in the weeks after the start of treatment, but there was no substantial reduction in tumour size. There was no gross changes on ultrasound examination.

Phase 4 (Fig. 5)

A median laparotomy was performed. Pre- and post-operative hormone assays are shown in Fig. 5. Ovarian vein blood was not obtained during the operation. A large multiple cystic tumour of the left ovary was found (Fig. 6). The right ovary and the uterus were macroscopically normal. Unilateral ovariectomy was performed. The histopathologic diagnosis was: well-differentiated Sertoli-Leydig cell tumour (Fig. 7). Endocrinological values became normal post-operatively.

Discussion

Virilization in pregnancy is a complex problem. In addition to ovarian and non-ovarian causes of virilization in the non-pregnant woman, other causes may be seen in pregnancy such as luteoma of pregnancy and hyper-reactio luteinalis (Ireland and Woodruff 1976). The luteoma of pregnancy is a solid androgen producing tumour which causes virilization of the mother and often the newborn female baby. In hyper-reactio luteinalis, both ovaries are enlarged and contain multiple cysts. The ovaries in hyperreactio luteinalis bear some morphological resemblance to the ovarian hyperstimulation syndrome. It is thought to be an 'overreaction' to β-hCG stimulation in pregnancy. Hyper-reactio luteinalis is more frequent in women with hydatidiform mole, choriocarcinoma and multiple pregnancy because these women produce more β-hCG.

Sertoli-Leydig cell tumours (SLCT) are uncommon neoplasms of the ovary and account for less than 0·5% of all ovarian tumours. Steroid synthesis in these tumours has been studied (Goslar 1984). An SLCT is a well-known cause of virilization (Roth *et al.* 1981), but has very rarely been reported during pregnancy. Pregnancy in women with a pre-gestational SLCT, though rare, has been described (Galle *et al.* 1978, Moltz *et al.* 1983).

In our patient the onset of virilization occurred during pregnancy when a very large multiple cystic mass was seen on ultrasound and CT scan. Normal ovaries were not seen. The tumour was considered to be bilateral. Elevated testosterone levels were found. These findings led us to the diagnosis 'hyperreactio luteinalis'. Efforts were made to prove the bilateral ovarian origin of testosterone, but because blood could be collected only from the left ovarian vein it remains uncertain whether testosterone overproduction took place only in the left or in both ovaries. Consequently we do not know whether the tumour was originally bilateral or unilateral.

Two possible explanations arise. Firstly, one might argue that there was a coexistence of a SLCT with a (bilateral) hyperreactio luteinalis. The normal postpartum drop of β-hCG levels (Haenel *et al.* 1986) was followed by a decrease of serum testosterone levels. Simultaneously the ultrasound image of the tumour changed, the multiple small cystic masses disappeared and the tumour became more solid although some large cysts persisted. The ultrasound findings and the tumour response to hCG might favour the original hypothesis of hyperreactio luteinalis.

Secondly, this tumour may have originally been a unilateral SLCT. The history supports this hypothesis: the sudden onset of virilization after 31 weeks gestation is suggestive of a neoplasm. SLCT has, although rarely, been reported to occur during pregnancy (Young *et al.* 1984). The persistence of the tumour post partum also favours the SLCT theory, although temporary coexistence of the SLCT and hyperreactio luteinalis remains possible. Since no similar cases are reported in the literature the changes in the ultrasound appearance of the tumour cannot be explained. The clinical findings suggest that a SCLT can be stimulated by hCG and that a 'stimulated' SLCT is different from a 'suppressed' SLCT. A gonadotrophin-dependent (Krukenberg) tumour causing virilisation during pregnancy has been reported (Connor 1968).

The endocrinological findings during treatment with oral contraceptives and then with a LHRH-analogue also support the 'stimulated' SLCT theory: the tumour continued to react to gonadotrophins with testosterone production. Low testosterone levels in these phases of treatment would be explained by suppressed gonadotrophins and consequently a lack of tumour stimulation. The treatment with buserelin demonstrates even more clearly the effect of gonadotrophins on the androgen production of this tumour. The administration of a LHRH-analogue was initially followed by rising levels of gonadotrophins and testosterone without apparent ultrasonic changes of the tumour. Later low levels of gonadotrophins and testosterone was found.

During the treatment with an oral contraceptive there was a rise in progesterone levels. This might either be a direct effect of gonadotrophins on theca cells thus causing luteinizing effects or it might also be explained as a consequence of conversion of precursors to progesterone. Finally, ovariectomy was performed. A return to normal endocrine functions was illustrated by the immediate resumption of a normal menstrual cycle. This has been described as one of the early signs of restoration of normal endocrine function after removal of a SLCT.

Fortunately the tumour was benign. Although malignant SLCT is rare, metastases have been reported (Pride *et al.* 1982). It is clear that if the tumour was originally a unilateral 'stimulated' SLCT the choice of treatment would have been ovariectomy. However, the large cystic and seemingly bilateral appearance of this tumour, possibly caused by coexistence of SLCT and hyperreactio luteinalis, obscured this diagnosis. This rare finding together with the patient's rejection of surgical therapy made it possible to investigate this exceptional case thoroughly.

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SHORT COMMUNICATIONS

Uterine rupture in midtrimester abortion. A complication of gemeprost vaginal pessaries and oxytocin. Case report.

J. J. Wiener, A. S. Evans *Department of Obstetrics and Gynaecology, University Hospital of Wales, Heath Park, Cardiff*

A 24-year-old woman gravida 4, para 3, whose three previous pregnancies were uncomplicated, was admitted at 16 weeks gestation for termination of pregnancy under the provisions of the 1967 Abortion Act. Gemeprost (16, 16-dimethyl-trans $\Delta 2$ prostaglandin E_1 methyl ester) 1 mg vaginal pessaries were inserted into the posterior fornix at 3-h intervals. After the second pessary she developed some lower abdominal pain controlled with co-dydramol. There was no vaginal bleeding. The total dose of gemeprost in the first 24-h was 5 mg.

Another course of gemeprost pessaries was given the next day. Contractions became established and there was slight vaginal bleeding The cervix remained closed. During the second course of five pessaries she received four 15 mg doses of intramuscular papaveretum. On the third day the patient had an ultrasound scan which revealed an apparently intrauterine pregnancy of 16 weeks gestation with no fetal heart beat. Vaginal bleeding was minimal. Oxytocin infusion 20 i.u. in 1000 ml of 5% dextrose was given by intravenous infusion at an initial rate of 10 drops per minute, increasing every 20 min by 10 drops/min to a maximum rate of 40 drops/min. The total dose of 50 i.u. of oxytocin was given over a period of 22 h.

By the fourth day the patient still had not aborted but was comfortable and mobile. She was pale and her lower abdomen was tender with minimal rebound tenderness and guarding. Vaginal examination revealed a large bulging lower uterine segment anteriorly and a closed cervix posteriorly. The haemoglobin concentration had fallen from 11.4 g/dl on admission to 6.5 g/dl. The diagnosis of uterine rupture was made and the oxytocin infusion was stopped.

At laparatomy the uterus was deviated to the right by a large left broad ligament haematoma extending anteriorly under the vesico-uterine peritoneum into the right broad ligament. There was a 4–5 cm diameter defect in the left anterolateral aspect of the uterus and the fetus had been extruded entirely into the broad ligament with the placenta still in the uterus. There was no free blood in the peritoneal cavity. It was not possible to conserve the uterus therefore a total abdominal hysterectomy was performed. The patient was given a transfusion of four units of whole blood. She made an uneventful post-operative recovery and was discharged home on the sixth day. Her haemoglobin level before discharge was 11.6 g/dl.

Discussion

Uterine rupture is an uncommon complication of termination of pregnancy but it has been reported with other prostaglandins following intra-amniotic—(Wentz *et al.* 1973; Lowensohn & Ballard 1974; Duenhoelter & Gant 1975; Propping *et al.* 1977), intravenous—(Smith 1975), intramuscular—(Vergote *et al.* 1982) and vaginal—administration (Sandler *et al.* 1979).

Transverse rupture of the cervix at the cervico—isthmic junction characteristically occurs in nulliparous women when prostaglandins are administered alone (Wentz *et al.* 1973; Duenhoelter & Gant 1975) or in combination with oxytocin (Lowensohn & Ballard 1974). Uterine rupture is more likely in multiparae (Propping *et al.* 1977, Sandler *et al.* 1979), especially those with a uterine scar stimulated with a combination of prostaglandins and oxytocin. The manufacturer of gemeprost (May & Baker) recommends a maximum total dose of 10 pessaries. Failed terminations with 10 gemeprost pessaries do occur (Cameron *et al.* 1987).

Lauersen *et al.* (1976) recommended ultrasound examination in the management of failed prostaglandin abortions. In their series of 529 pregnancies 10 (1·9%) failed to abort and in seven of these ultrasound revealed either uterine myomas distorting the uterus or congenital uterine abnormalities. An ultrasound scan did not detect uterine rupture or any other abnormality in our patient but the scan was done by a relatively inexperienced operator.

We do not know when the uterus ruptured but we assume that it was durng the second course of gemeprost because she had uterine contractions and vaginal bleeding with no cervical dilatation then, and an ultrasound scan subsequently showed no fetal heart beat. The definitive diagnosis was only made during the oxytocin infusion, when the haemoglobin concentration had dropped to 6·6 g/dl.

We believe that this is the first report of uterine rupture associated with the combination of gemeprost and oxytocin. The absence of any earlier report probably reflects the small number of pregnancies terminated in the second trimester with gemeprost, as the product has only relatively recently been used for this purpose.

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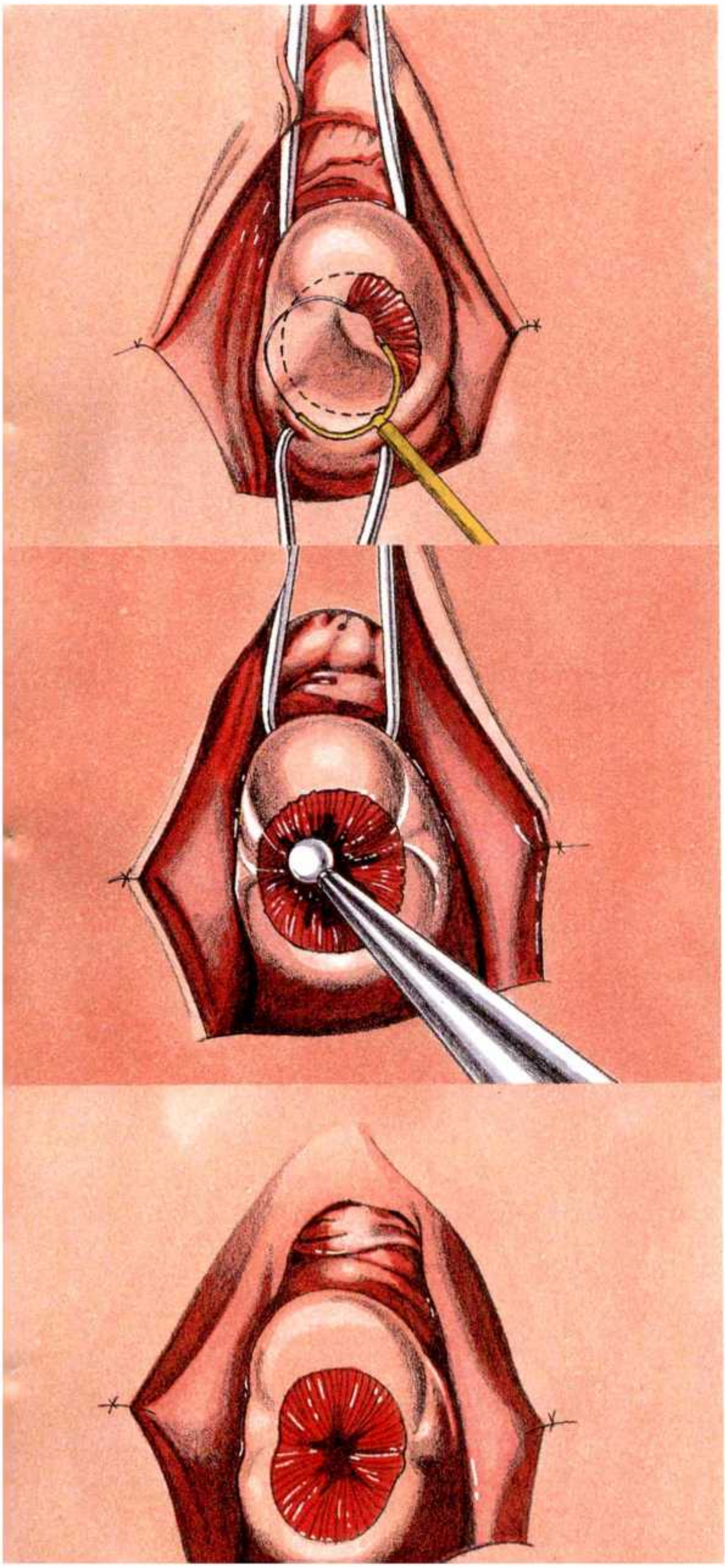

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CORRESPONDENCE

The treatment of detrusor instability in post-menopausal women with oxybutynin chloride: a double blind placebo controlled study

Dear Sir,

We were interested to read the recent report by Tapp *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 521–526] regarding the value of oxybutynin in post-menopausal women. Hopefully their further testimony to the efficacy of oxybutynin in idiopathic instability will serve to expedite the long-overdue product licence for this drug.

We have recently completed a placebo-controlled cross-over trial of oxybutynin, 3 mg, for idiopathic instability in women of any age (Moore *et al.* 1990). We would agree with the authors' comment that the dosage of 5 mg four times daily used in their trial was probably too high. Of 53 patients enrolled in our study using the 3 mg thrice daily regimen, only 7·5% discontinued the trial because of unpleasant side-effects, thus we have come to regard the lower dose tablet as quite acceptable to most patients.

Previously oxybutynin has acquired an unfortunate reputation for producing an increase in residual urine volume, which Tapp *et al.* listed as one of their main findings. Using the 3 mg thrice daily regimen, we showed little increase in residual urine volume and have not found this to be a clinically important effect of oxybutynin.

Finally we have a question about the authors' statistical treatment of their data. The comparative efficacy of oxybutynin over placebo was shown (Table 6) by calculating the mean difference in cystometry variables for all 21 patients after oxybutynin, regardless of whether they had received active drug as the first (nine patients) or the second (12 patients) treatment.

Our study showed a significant carry-over effect in patients who were given oxybutynin first: despite a 1-month washout and a 1-month placebo period, cystometry values did not return to baseline if the patients were given oxybutynin first. Thus any method of analysis which does not separate the data by order of treatments is likely to underestimate the difference between active drug and placebo.

We mention this because the authors pose an important question about the clinical significance of detrusor contractions provoked by standing. Because such contractions were abolished by placebo in six of seven patients, Tapp *et al.* suggest that detrusor contractions during standing provocation may be an artefact.

Before questioning the validity of standing-provocation cystometry, which has been a mainstay of urodynamic practice for many years (Arnold, 1974; Mayo 1978), it would be important to know how many of these six patients had placebo as the second treatment. If they had received oxybutynin as the first treatment, then quite possibly during the subsequent placebo period, the lack of detrusor contractions seen during standing provocation may simply reflect an oxybutynin carry-over effect.

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Author's reply

Dear Sir,

We would like to thank Kate Moore and colleagues for raising some important issues about our study of oxybutynin chloride and its use in the treatment of detrusor instability in post-menopausal women. We concluded that the dosage of 5 mg oxybutynin four times a day was excessive as it resulted in a very large number of side effects. We have no doubt that 3 mg of oxybutynin chloride three times a day would be more acceptable to patients, however, we await Dr Moore's paper to see if the efficacy of the drug is maintained at the lower dose.

Our cross-over study was designed using the available pharmacokinetic information on oxybutynin chloride. A 2-week washout period was therefore chosen. When we initially analyzed our data we were surprised to find that placebo therapy was associated with a significant fall in the height of the highest unstable contraction when compared with pre-treatment values. In order to try and explain this unexpected finding we did perform a separate analysis of our data to see if the order of drug treatment was relevant. We did not identify the carry-over effect mentioned by Dr Moore *et al.* in their letter. More specifically the six of our seven patients who apparently had their detrusor pressure rise provoked by standing abolished with placebo were not restricted to those patients who received oxybutynin first. Indeed three of the six received placebo as their first treatment.

Detrusor instability is subject to spontaneous exacerbations and remissions and has a high placebo response rate. The carry-over effect that Moore *et al.* report must therefore be taken in context with these factors.

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Has in-vitro fertilization made salpingostomy obsolete? (Commentary)

Dear Sir,

We were puzzled by Lilford and Watson's Commentary [*Br J Obstet Gynaecol* (1990) **97**, 557–560]. They compare on the one hand present day results for *in-vitro* fertilization (IVF) with success rates for tubal surgery in Leeds as described by Watson *et al.* (1990). That study looked at the outcome of 83 operations carried out by 10 different surgeons in two different hospitals over a 7-year period 1980–86. This would suggest that each surgeon is operating on either one or two patients a year. The overall live birth rate is quoted as 11%. The comparable Leeds IVF birth rates are not quoted and as far as we are aware, more recent IVF results also remain unpublished.

We work in an ordinary, basic District General Hospital on a three consultant unit, providing a full range of services including tubal surgery. Over the last 10 years one of us (M.B.) has carried out over 600 microsurgery operations. We now operate on 75–100 patients a year, roughly the same number of patients a year as the Leeds experience over the 7 years quoted. Our livebirth rate per patient for the first 210 unselected cases (1979–84) is 22%. We have had over 150 livebirths over the last 10 years.

We would agree that the results for hydrosalpinges are disappointing. Of our first 210 patients 60 had bilateral salpingostomy with only 8% livebirth rate. However, no patient was refused surgery on the basis of age or degree of tubal damage. A more detailed analysis of hydrosalpinges in selected patients suggested that livebirth rates are up to 30%.

However, Lilford & Watson quote a Leeds livebirth rate of 5% for hydrosalpinges. Using this figure and comparing it with current IVF results, they commend IVF rather than microsurgery to purchasing authorities. A more realistic approach would be to keep all options open.

The lessons we have learnt from the last 10 years is that neither IVF nor mircosurgery will solve most women's tubovarian induced infertility. Good results involve dedicated microsurgeons and large teams of specialists servicing IVF programmes. As IVF results improve there may be less emphasis on microsurgery but we suspect that nationally this will prove to be a slow, expensive, frustrating process over the next 20 years. The prospect of a comprehensive, reliable national IVF service is decades away, if ever attainable.

Unfortunately, nowhere in their commentary do the authors give an example of a British unit's cost per IVF treatment combined with the same unit's livebirth rates. A reasonable approximation for the national figure assuming a 10% livebirth rate and costs per treatment cycle of about £1500 a cycle, would be £15 000 per livebirth.

In our experience most hydrosalpinges are operable in a technical sense. Indeed in most cases estimates as to the prospects of success are considerably influenced by the operative findings and individual surgical techniques required. Only about 4% of all tubovarian problems are suitable for laparoscopic salpingostomy.

Excluding patients over the age of 35 or those with extensive, dense tubovarian adhesions, you could reasonably expect livebirth rates of 15% (most series from specialist units quote a 15–20% livebirth rate).

The length of stay for patients having tubal surgery in Leeds is quoted as 10 days, costing in excess of £1000. Our patients stay in hospital for 6–7 days but on the other hand spend 2–5 h in the operating theatre. These two variables cancel each other out. This suggests a cost per livebirth for each patient with hydrosalpinges of £6667 and the average cost of a livebirth for all our patients of £4545, one-third of the current cost for IVF.

The reality is not so simple, since we do not have the trained microsurgeons to achieve these results nationally. However, the potential is there, provided that surgery is carried out by those regularly operating on a large number of patients.

Before deciding what is the 'best buy', purchasing authorities should look at established success rates locally and encourage initiatives for IVF and microsurgery at regional level.

If we were the purchasing authority in Leeds, we suspect we would go out and buy a microsurgeon.

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Sir,

Professor Lilford and his colleagues, in their Commentary and article [*Br J Obstet Gynaecol* (1990) **97**, 557–560; 561–568], make a plea for the wider availability of NHS funded IVF centres, with which most gynaecologists will agree. They go on to advocate IVF as the first line of treatment for most women with distal tubal occlusion.

Most women with tubal infertility, given the choice, opt for surgery rather than IVF which they regard as the last resort. Professor Lilford's Table 2 (pp 564–5) is somewhat selective. A fairer survey of the results of surgical treatment for distal tubal occlusion is that of Lavy *et al.* (1987). They summarize the results of neosalpingostomy from 18 publications; 1193 patients achieved 325 pregnancies (27%) with an ectopic pregnancy rate of 6·9% which is not much different from that seen in IVF centres.

Such results can be achieved by most tubal surgeons provided women with dense adhesions, multiple blockages and hopelessly thickened chronically inflamed tubes are excluded. Once a patient has achieved a pregnancy following surgery, further pregnancies usually follow with ease and no further treatment or expense.

Furthermore the authors fail to realize that the results in distal tubal surgery depend very much on the aetiology of the occlusion. Hydrosalpinges resulting from pelvic peritonitis after perforated appendicitis usually do well: the endosalpinx is intact and the fimbriae displayed at operation are usually excellent. Gonococcal disease on the other hand, due to its translumenal spread, has a poor prognosis. Incidentally many of these patients may take up to two years to become pregnant after surgery and even 40 months' follow-up does not give the true picture.

The overwhelming need at the present time is to direct resources to the better education of yong people to prevent sexually transmitted diseases and their sequelae; to provide better services for the investigation and treatment of infertility generally, and to encourage more widespread training and distribution of gynaecologists with a special interest in infertility surgery. Ignoring these needs and instead establishing more IVF centres is unlikely to be cost effective in the long run.

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Author's reply

Dear Sir,

Burke & Nwosu give overall results for tubal surgery which are not much better than those achieved in Yorkshire (Watson *et al.* 1990). What about their results for salpingostomy, since our editorial is concerned with this operation? Their experience with 'hydrosalpinges' is, within standard confidence limits, as bad as ours. Both Burke & Nwosu and Reiss assert that, if better selection is practised, then the results for salpingostomy will be much better—we would ask them all to read our article again. This is precisely what we advocate. However, we go on to say that patients with good prognostic features (which would include a small number arising from ectosalpingitis) make up a small proportion of all patients with tubal blockage. Hence the value of IVF for most patients with blocked tubes following gonococcal and chlamydial destructive damage. While emphasizing that the results of selective tubal surgery depend on patient selection, Burke & Nwosu are quite happy to quote overall (i.e. unselected) success rates for IVF even though these are extremely sensitive to the cause of the infertility. For example the prospects for pregnancy with IVF are much better for younger women with tubal blockage. The costings based on the above authors' estimates of success are therefore specious.

Furthermore, your correspondents make the error, which we warned about in our Commentary, of mistaking a price for a cost and contrary to what they say, we do indeed quote *costings* for IVF in the United Kingdom and find that Burke & Nwosu have over-estimated these by a factor of almost three.

The writers state, without reference, that only 5% of 'tubovarian problems' are suitable for laparoscopic salpingostomy. Presumably they are referring to patients with bilateral distal tubal obstruction; if so they will provoke howls of protest from minimally invasive surgeons supported by the authoritative reference which we quote. Tubes which cannot be opened laparoscopically have poor prognostic features for open surgery and such patients should be referred directly for IVF. Sadly they are the majority in both our series—witness the poor overall results quoted by Burke & Nwosu with their much better results in patients with good prognostic features. The data quoted in our full paper (Watson *et al.* 1990), along with randomized trial evidence (Rock *et al.* 1984), do not support the idea that microscopic surgery improves pregnancy rates in women with damaged tubal blockage.

Your first correspondents' departure from data into conjecture reaches its climax in the last paragraph, where they claim that Leeds managers should buy microsurgery. This judgement should be informed by the success of IVF for similar patients in our city or nearby centres. Surely your correspondents would need to obtain this current information before making such a statement. If they had done this, they would have found that our ultrasonically confirmed pregnancy rate for tubal factor infertility in the current financial year is 22% per cycle initiated (*n*=27), 24% per oocyte retrieval and 30% per embryo transfer. We think that the correct treatment for bilateral distal tubal blockage is endoscopic salpingostomy at the time of initial laparoscopy, which should be done by a doctor with an interest in infertility. Resources are best used by proceeding to IVF, either directly, if minimally invasive surgery is not technically feasible, or after an appropriate delay if pregnancy is not achieved in the remaining cases.

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BOOK REVIEWS

Oral Contraceptives and Breast Cancer edited by R. D. Mann. Parthenon Publishing, Carnforth, Lancs and New Jersey, USA, 1990, 406 pages with figures and tables, £45.00

This book is a record of the proceedings of a symposium held at the Royal Society of Medicine, London, in July 1989. Twenty three authoritative epidemiologists and clinicians presented data to try to define and quantify a possible association between the use of the combined oral contraceptive (COC) and breast cancer. The size of the book testifies to the extent of research into this issue which is at the heart of the burden women bear in fertility control.

The book starts with an excellent overview of our current knowledge, acknowledging the difficulty in explaining the discrepancies between various studies.

The bulk of the book is dedicated to extensively referenced accounts and updates of the epidemiological work of the past two decades. Each chapter is followed by a discussion cleverly edited and containing several gems of thought and reasoning. However to follow some of the discussion the reader needs to be familiar with 'confounding variables', 'multivariate logistic regression', 'confidence limits', and so on.

An overview of the benefits and risks of COCs (chapter 7) puts the breast cancer issue in a wider health perspective. This chapter is essential reading for those advising on or prescribing COCs.

The last quarter of the book deals with practical aspects of management. There is a stimulating chapter looking at hormonal manipulation that may reduce the risk of breast cancer. Research strategies for the future are also addressed.

The book ends with Sir Richard Doll's Careful Conclusions and Clear Recommendations. He found the data reassuring on COC use in a woman's mature years. But the fact that all studies presented showed a relative risk of one or more for breast cancer in the under 35s if they used the pill at a young age for over 4 years led him to conclude that a risk exists and must be discussed with prospective users especially the young. He emphasized the need for more research and longer term studies.

This book is an important resource for those with an academic interest in the epidemiology/biology of breast cancer. More importantly it provides the basis on which women can be given the information to allow them to make an informed choice in contraception.

A. Kubba

Recent Advances in Obstetrics and Gynaecology. Number 16 edited by John Bonnar. Churchill Livingstone, Edinburgh, 1990, 296 pages with figures and tables, £19.95

This 16th issue of Recent Advances appears some 63 years after the publication of the first. In this volume the editor, John Bonnar, says that the book is becoming so popular that in future it is to be published every two years. Essentially practical volumes these are for the registrars and consultants in all countries to read in order to keep up with the growth points in our speciality.

Trophoblastic disease in Hong Kong is discussed by those who have a great experience of the disorder. The problem of the immunology of recurrent miscarriage is clarified for us and the author sagely advises more double-blind trials to test whether immunotherapy is effective with a salutary note that patients with abnormal-shaped uteri should first be excluded from such trials. For me, the chapter on Doppler studies in pregnancy clarified a difficult subject. The problems presented by AIDS are discussed and, in future, no volume will be complete without dealing with this alarming problem. All practising obstetricians and gynaecologists should read the chapter on medicolegal problems on 1st of January each year.

The gynaecological chapters include cervical screening, carcinoma of the cervix, acute pelvic inflammatory disease and hysteroscopy. All these are useful. The chapter on Stress in Infertility was illuminating although I would have liked to have seen the stress on doctors, as well as that of patients, mentioned

The three updating chapters on Hormones are all well produced and instructive.

The volume really needs no review; all of us could usefully buy a copy.

John M. McGarry

Infections in Pregnancy edited by Larry C. Gilstrap III and Sebastian Faro. Alan R. Liss Inc, New York, 1990, 277 pages with figures and tables, $58.00

The major goal of this book, according to the editors' preface, is to 'provide the practising clinician with recent information regarding the more common infections encountered in obstetrics as well as a few not so common but important infections'. It is hard to take this claim seriously when the book omits any reference to such important infections in pregnancy as rubella, listeriosis and, in the 'less common' category, HTLV1.

The book is clearly aimed at North American clinicians—most of the incidence and prevalence data provided are exclusively those pertaining to the USA (e.g., for syphilis, AIDS/HIV, toxoplasmosis) and this national bias may be confusing when the advice given differs from that accepted in the UK. For example, the time period of onset of maternal chickenpox pre- and post-delivery when varicella zoster immunoglobulin is recommended for the neonate is considerably shorter in the chapter on this infection than that specified in the current UK Department of Health recommendations.

The potential strength of Infections in Pregnancy is the inclusion of infections relevant to the mother as well as those affecting the fetus. There are excellent chapters on soft tissue infections, pregnancy and septic shock, episiotomy infection and dehiscence and post partum endometritis; there are also useful general contributions on antimicrobials and pregnancy, and on the microflora of the genital tract.

Unfortunately, however, these strengths do not outweigh the weaknesses: in addition to the criticisms outlined above, the editing is patchy. Some chapters have summaries, others do not; the ordering of chapters has little apparent logic; the balance of information is uneven—the chapter on protozoal infections includes two and a half pages on toxoplasmosis, a relatively common infection of considerable current interest, compared to nearly three pages on leishmaniasis and five pages on trypanosomiasis! There is conflicting advice within one chapter: silver nitrate drops are recommended for chlamydial ophthalmia neonatorum on one page but declared ineffective on another.

In summary, this book which at first sight looked a promising and useful new guide for obstetricians turned out to be disappointing and unlikely to be helpful, especially in British obstetric practice.

Susan M. Hall

AIDS in Gynecology (Clinical Practice of Gynecology Vol. 1 No. 1) edited by Newton G. Osborne. Elsevier, New York, Amsterdam, London, 1989, 144 pages, with figures and tables, $35, Dfl90.

AIDS in Gynecology is the first volume in a new series edited by Baggish entitled Clinical Practice of Gynecology. This small volume has the collected view of many experts of this dreadful disease which is now entering the clinical practice of most of us in the UK. At a recent RCOG meeting, a show of hands produced a 50% response rate to the question: 'How many of you have come across a case of AIDS?' Now that heterosexual transmission of this disease is increasing more than in other groups, it is becoming more relevant to gynaecologists and their practice. In this little book we have a pocket companion of instruction which we all need to read. The chapter on the 'Impact of AIDS on Gynecology' has particular importance and contains such statements as 'AIDS had forced physicians to analyse their own obligations to an afflicted individual. This has entailed the weighing of personal risk versus professorial duty'. Such risks have been accepted by doctors in the past; but AIDS has pushed some to question this attitude.

Without being alarmist, the chapter on epidemiology paints a terrifying picture of the future unless a cure is found.

My only real criticism of the book is the authors' excessive reliance on acronyms—but I suppose, as with every new disease, we will have to force ourselves to digest these new abbreviations.

I think this volume will become an essential addition to every gynaecological library.

John M. McGarry

Books received some of which will be reviewed at a later date

Early Pregnancy Failure (Clinical Obstetrics and Gynaecology) edited by H. J. Huisjes & T. Lind. Churchill Livingstone, Edinburgh, 1990, 278 pages illustrated with figures and tables, £45.00

Gynecology. A Practical Approach by Victor Gomel, Malcolm G. Munro & Timothy C. Rowe. Williams & Wilkins, Baltimore, Hong Kong, London, Sydney, 1990, 332 pages with figures and tables, paperback £26.00

Hysterosalpingography: Techniques and Interpretation by Robert B. Hunt & Alvin M. Siegler. Year Book Medical Publishers, Inc. Chicago, London, Boca Raton, 1990, 186 pages fully illustrated, £59.00

Diagnostic Ultrasound of Fetal Anomalies: Text and Atlas by David A. Nyberg, Barry S. Mahony & Dolores H. Pretorius. Year Book Medical Publishers, Inc. Chicago, London, Boca Raton, 1990, 778 pages fully illustrated, £127.50

Obstetrical Events and Developmental Sequelae edited by Nergesh Tejani. CRC Press, Inc. Boca Raton, Florida, 1990, 202 pages with figures and tables, £76.00

Kistner's Gynecology. Principles and Practice Fifth edition, edited by Kenneth J. Ryan, Ross Berkowitz & Robert L. Barbieri Year Book Medical. Publishers, Inc. Chicago, London, Boca Raton, 1990, 750 pages fully illustrated, £59.00

Injectable Contraceptives. Their Role in Family Planning Care World Health Organization, Geneva 1990, 117 pages, Sw fr. 21

Postreproductive Gynecology edited by Hugh M. Shingleton & W. Glenn Hurt. Churchill Livingstone, New York, Edinburgh, London, Melbourne, 1990, 528 pages, 120 illustrations, £60.00

Congenital Malformations. Antenatal Diagnosis, Perinatal Management and Counseling by John W. Seeds & Richard G. Azizkhan. Aspen Publishers Inc. Rockville, Maryland, 1990, 390 pages illustrated. £56.00

A Child is Born photography by Lennart Nilsson text by Lars Hamberger. Doubleday, London, New York, Toronto, 1990, 213 pages fully illustrated with colour plates, £14.95

The Female Breast and Its Disorders edited by George W. Mitchell, Jr & Lawrence W. Bassett. Williams & Wilkins, Baltimore, Hong Kong, London, Sydney, 1990, 294 pages fully illustrated, £55.25

Baillière's Clinical Obstetrics and Gynaecology. Medical Induction of Abortion. Volume 4 No 2, June 1990 edited by M. Bygdeman. Baillière Tindall, London, Philadelphia, 235–418 pages with figures and tables, £22.50 single issue, £49.00 annual subscription

Assisted Human Conception (British Medical Bulletin Volume 46 Number 3, July 1990) edited by R. G. Edwards. Published for the British Council by Churchill Livingstone, 565–850 pages. Single copy £27.50, annual subscription £80

ABC of Sexually Transmitted Diseases. Second edition by Michael W. Adler. British Medical Association, London, 70 pages fully illustrated with colour plates UK £10.95, Abroad £13.00 including postage

Proceedings and Symposiums

Establishing A Successful Human Pregnancy Serono Symposia Publications from Raven Press Volume 66 edited by R. G. Edwards. Raven Press, New York, 1990, 300 pages with figures and tables $79 50

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COMMENTARIES

Can the withdrawal bleed following oestrogen replacement therapy be avoided?

Hormone replacement therapy in the short-term relieves menopausal symptoms and in the long-term minimizes osteoporosis (Christiansen *et al.* 1980, Savvas *et al.* 1988) and heart disease (Ross *et al.* 1981). However, for those women with an intact uterus the need for a regular progestogen-induced withdrawal bleed, which may be painful, heavy, and associated with premenstrual-like symptoms, often limits the acceptability of oestrogen therapy. Is there a way of avoiding this cyclical bleeding?

The use of unopposed oestrogen therapy in the 1960s and 1970s led to an increase in endometrial hyperplasia (Studd & Thom 1981) and cancer (Smith *et al* 1975, Ziel & Finkle 1975). There is a 7% prevalance of cystic hyperplasia with low-dose cyclical oral therapy and this rises to 15% with high-dose cyclical oral therapy (Sturdee *et al.* 1978). Cystic hyperplasia is associated with irregular heavy bleeding and has a small but significant risk (1%) of progression to endometrial cancer. Atypical hyperplasia, also produced by unopposed oestrogens, carries a greater risk of up to 45%, depending on the severity of the atypia.

The proliferative effect on the endometrium of unopposed oestrogens can be prevented and usually reversed by cyclical progestogens. Thom *et al.* (1979) reported that norethisterone, 5 mg daily, taken cyclically for 21 days a month for 3 months converted the endometrium of all women with cystic hyperplasia back to normal. There was no such guarantee of a return to normality from atypical hyperplasia, although this did occur in most women.

This protective effect of adding progestogens to oestrogen therapy is now accepted to such an extent that it is incorporated into many hormone regimens, and unopposed oestrogens are considered to be forbidden treatment for postmenopausal women with a uterus. This has resulted in a marked reduction in the occurrence of hyperplasia. Perrson *et al.* (1989) have confirmed that the excess risk of endometrial malignancy is removed with the use of combined oestrogen and progestogen. This anti-proliferative effect of progestogens is duration dependent with 3% of women having cystic hyperplasia with 7 days of progestogen therapy, 2% with 10 days and none with 13 days of progestogen (Sturdee *et al.* 1978, Paterson *et al.* 1980).

However, the addition of a progestogen to oestrogen therapy is not without problems, as a large percentage, up to 20–30%, develop symptomatic side-effects of breast tenderness, nausea, irritability and water retention during the latter part of the progestogen course. These side-effects, which are much like the symptoms of premenstrual syndrome (Magos *et al.* 1986), often limit the acceptability of progestogens and the duration of time which a woman is prepared to tolerate the symptoms. Hence shorter courses of progestogen may be taken and these may increase the risk of developing endometrial pathology and irregular bleeding.

There are also unwanted metabolic changes in that progestogens decrease high density lipoproteins (HDL), increase low-density lipoproteins (LDL) and, theoretically, can remove some of the cardioprotective effect of oestrogens. The ultimate disadvantage of cyclical progestogens to the women is the withdrawal bleed, which may be heavy, painful and associated with the progestogenic premenstrual-syndrome like symptoms.

This trio of metabolic side-effects, cyclical symptoms and the necessity to have a withdrawal bleed, limits the acceptability of oestrogen replacement therapy and may be the principal reason why women do not start or do not continue oestrogen therapy for an adequate length of time. These problems do not occur if the woman has had a hysterectomy as such women are able to take unopposed continuous oestrogens, but for the woman with a uterus it is necessary to have other options available.

The use of continuous combined oestrogen and progestogen preparations have shown encouraging results in the production of an atrophic endometrium and in the elimination of uterine bleeding. The initial study by Staland (1981) used a fixed daily dose of both oestrogen and progestogen and involved both peri-menopausal and post-menopausal women. After 3 months, this treatment resulted in amenorrhoea in 36% of the peri-menopausal women and 73% of the post-menopausal women. After 6 months of treatment this had increased to 60% and 87%, respectively. Those women who were still experiencing some uterine bleeding after 6 months reported that the blood loss was both lighter and of a shorter duration than their normal periods.

Magos *et al.* (1985) attempted to prevent this uterine bleeding by increasing the progestogen dose at 3-month intervals if any bleeding had occurred in the preceding 3 months. By 3 months 65% of those on the lower dose and 47% on the higher dose of oestrogen had become amenorrhoeic. After 1 year of treatment 95% of the women left in the study had amenorrhoea, but there had been a 33% drop-out rate for varying reasons, not always due to irregular bleeding. Sporrong *et al.* (1988) treated a series of post-menopausal women with a fixed dose of oestrogen and two doses of two continuous progestogens and showed that amenorrhoea was achieved in up to 50% of women (range 7–50%) at 3 months, and up to 91% (range 77–91%) at 1 year.

It remains uncertain which is the ideal starting dose of progestogen to achieve amenorrhoea, but once amenorrhoea is established it is possible to decrease the daily dose of progestogen. It is probably advisable to start with a lower dose of oestrogen and a higher dose of progestogen, as this achieves amenorrhoea more quickly, and to modify the dose subsequently to maximize the oestrogen response without increasing the progestogenic side effects.

Endometrial biopsies in those women with amenorrhoea showed either an atrophic or hypoplastic endometrium, and those with uterine bleeding also had an inactive endometrium with no abnormal pathology. Continuous combined oestrogen and progestogen preparations are adequately protective to the endometrium in the short-term but the long-term effects are unknown, as only Magos *et al* (1985) have studied women after 18 months of treatment. These women need endometrial sampling if irregular bleeding occurs after amenorrhoea has been achieved, as endometrial cancers, if they do occur in an atrophic endometrium, are usually of a more malignant nature than those juxtaposed to a hyperplastic endometrium (Christopherson 1986).

The metabolic effects of continuous combined oestrogen and progestogen preparations are becoming clearer. Three studies (Mattsson *et al.* 1984, Jensen *et al.* 1987, Christiansen & Riis 1990) have shown a significant reduction in both LDL and total cholesterol levels and a variable change in HDL levels, but no real change in the LDL/HDL ratio. As this ratio appears to be a good predictor of ischaemic heart disease, there is unlikely to be a detrimental effect on the cardioprotective value of oestrogens using these combined preparations.

There may also be added benefits of continuous progestogens in that they may stimulate bone formation (Christiansen *et al.* 1985). The study by Riis *et al.* (1988) confirmed that the continuous combined oestrogen and progestogen preparations had a positive effect on bone mass when compared with placebo. In this issue of the Journal (p. 1087) this group have reported a 5-year follow-up and are recommending continuous combined oestrogen and progestogen treatment as the ideal means of preventing osteoporosis without the inconvenience of a withdrawal bleed.

Is there a small place for unopposed cyclical oestrogens in selected patients with a uterus as up to 23% of women on such therapy do not bleed (Sturdee *et al.* 1978)? Although this treatment is now generally viewed as unacceptable, we believe that for those women who wish to avoid uterine bleeding or for those who are unable to tolerate progestogens, low-dose unopposed oestrogens may be given provided that the woman is aware that she may occasionally have breakthrough bleeding and that there is a small but definite risk of endometrial pathology. This is particularly relevant for the older post-menopausal women with pelvic atrophy or osteoporosis who refuses to accept any vaginal bleeding. All women receiving unopposed oestrogens should have careful counselling because of the potential clinical and medico-legal implications of this type of treatment. They must be prepared to undergo an endometrial biopsy approximately every 2 years.

Recent developments in the treatment of menorrhagia have led to the use of the resectoscope or laser to destroy the endometrium in an attempt to induce amenorrhoea. The results in the pre-menopausal women are encouraging in that 50–70% achieve amenorrhoea (Goldrath *et al.* 1981, Magos *et al.* 1989), despite the fact that many of those women who develop amenorrhoea still have pockets of endometrium on follow-up endometrial sampling. If it were possible to ensure total endometrial ablation it would be feasible to use the same technique on the post-menopausal woman and then prescribe unopposed oestrogens. However, the current view is that progestogens must still be added because these remaining areas of endometrium are at risk of overstimulation.

The place of endometrial resection in the treatment of the post-menopausal women requiring oestrogen replacement remains to be clarified by long-term studies in the appropriate population. The technique has dangers such as uterine perforation, fluid overload and anaesthetic complications. Greater awareness of the limitations of this interesting surgical procedure may well encourage the use of vaginal hysterectomy as an alternative means of treatment in the post-menopausal woman on oestrogen replacement who suffers from intolerable bleeding and progestogenic side effects. Such a development, already gaining some momentum, would need careful assessment of the balances between the long-term benefits of oestrogen-only-therapy and the short-term risks of surgery.

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Prenatal screening and diagnosis: Some psychological and social issues

The detection of possible fetal abnormality has become a major component of antenatal care and, in the wake of the new technology, there have been a number of studies of women's experiences. The emphasis of most studies has been on the extent to which women find prenatal screening and diagnosis stressful. A number of studies have also considered other psychological aspects, such as maternal attachment to the fetus, but many of these findings have been methodologically unsound. For example, the often quoted report of Fletcher & Evans (1983) that ultrasound hastens maternal bonding, was based on a sample of two. Most studies have been concerned with women undergoing alpha-fetoprotein (AFP) screening, amniocentesis or ultrasound scanning. All of these procedures have the potential both to allay anxiety and to create it: false positives in AFP screening, and the long wait for results from amniocentesis are both sources of stress, while the excitement of 'seeing' the baby is a unique feature of ultrasound (Green 1990).

The culmination of the screening process for those picked out as being 'at risk' is likely to be amniocentesis, carried out at approximately 16 weeks. Because chromosome analysis takes 3 to 4 weeks, terminations for genetic indications are unlikely to take place before the 20th week. In the UK in 1982, 26·3% of amniocentesis results were not available until 21 weeks or later and as a result 13% of terminations for genetic indications occurred as late as 22 weeks or even later (Timothy & Harris 1986). There are many studies attesting to the lasting trauma of terminating a pregnancy on grounds of fetal abnormality, particularly at this late stage (Blumberg *et al.* 1975; Donnai *et al.* 1981; Lloyd & Laurence, 1985).

Many of the reported adverse psychological effects relate to the relatively late stage of pregnancy at which amniocentesis is carried out. Chorion villus sampling (CVS) and early second trimester amniocentesis will mean that for some women the process can be brought forward. However, approximately two-thirds of Down's fetuses are thought to be miscarried in early pregnancy (Creasy & Crolla 1974). Ironically, earlier diagnosis will mean, therefore, more women being tested, more positive results and more terminations because an unknown proportion of these would have miscarried before amniocentesis would have been carried out at 16 weeks. Furthermore, early diagnosis is only of relevance to those women whose indication for amniocentesis is apparent at, or before, the start of pregnancy. The trend towards assessing Down's syndrome risk on the basis of maternal serum AFP as well as maternal age will decrease the numbers eligible for early diagnosis and increase the number whose candidacy for amniocentesis arises from routine screening procedures. These women will still have no alternative to second trimester amniocentesis, and it is precisely such women who find amniocentesis most stressful (Farrant 1980). Furthermore, results from a recent Canadian study suggest that, with something better to put in its place, second trimester amniocentesis now seems less attractive than it did 10 years ago (Spencer & Cox 1987; 1988).

Although different issues arise from different forms of prenatal screening, some common findings do emerge. To have doubt cast upon the health of the fetus is very stressful especially for a woman with no *a priori* reason to consider herself at risk. Whatever the benefits of screening there is no escaping the fact that anxieties will be created for a proportion of women whose fetuses are, in fact, healthy. Findings from other medical contexts (Bloom & Monterossa 1981; Rothenberg & Sills 1968) would suggest that doubts will persist long after false positives have been negated. Furthermore, in the case of AFP screening, the accumulation of data indicating that pregnancies with abnormal levels are at increased risk for a wide range of perinatal complications (Milunsky *et al.* 1989) will only increase the fears of women with 'false' positive results, particularly when it is unlikely that this fore-knowledge can be used in any useful way. The evidence linking anxiety in pregnancy with poor obstetric outcome (Reading 1983; Lederman 1984) should lead us to question whether we wish to create anxiety in 30 pregnant women in order to detect one neural tube defect, which arguably would, in any case, have been detected by a routine ultrasound scan. However, it is not clear how one can rationally calculate the arithmetic that says that it is worth making x no. of pregnant women anxious in order to detect one abnormal fetus. This is one of the dilemmas of any screening programme.

One issue that emerges very clearly from the literature is that of communication and the transmission of information. This is particularly important in AFP screening programmes which are often poorly understood (Faden *et al.* 1985; Marteau *et al.* 1988). Donnai (1987) argues that 'it should be ensured that all patients enter a screening programme with full knowledge of the tests and their limitations and having given some thought to their action if a test result suggests that further specific tests are indicated.' These conditions are rarely met. Counselling is more frequently encountered before amniocentesis and CVS, but even then it is more likely to occur for women taking part in randomized control trials or other pieces of research than in everyday practice. There is the danger that once the novelty of a new technique has worn off staff may stop taking the trouble to give explanations.

As well as the need for information *before* screening, the behaviour of the person carrying out the procedure is crucial. Roberts (1986), for example, found that the scan operator was the single most important determinant of women's satisfaction with the scan. The positive image of ultrasound that has been spread through the media has led women to expect a high level of feedback. If for any reason they do not get this they are likely to suspect the worst. Having notes placed in a sealed envelope without any communication taking place, for example, (Jacoby, 1988) confirms a woman's fears that her baby has a severe deformity. The position of radiographers is, of course, a very difficult one since the diagnostic procedure is taking place literally before the mother's eyes, but they are rarely authorized to communicate their findings to her.

The final phase of the diagnostic process in which communication is so important is imparting the results Farrant (1985) has drawn attention to a fundamental difference between what women and obstetricians think prenatal diagnosis is for. Obstetricians see it as being to detect abnormalities, women see it as being a means of reassuring them that the baby is all right. The clash between these perspectives is most obvious when it comes to transmitting negative results. In Farrant's study 80% of a sample of 323 consultant obstetricians rated the transmission of *positive* amniocentesis results as 'very urgent' while only 23% placed the same importance on communicating negative results. A quarter said that they usually waited until the next routine clinic appointment, and a few said that they did not usually inform women at all if their results were negative. This practice has been shown to perpetuate very severe levels of anxiety (Fearn *et al.* 1982).

The existence of prenatal diagnosis both reflects the values of our society and puts pressure on women to conform to those values (Rothman 1986). It is not considered acceptable to allow a newborn handicapped baby to die but it is deemed highly desirable to terminate an affected pregnancy. Indeed women who, rejecting the idea of abortion, decline prenatal diagnosis, may be seen as having brought their situation upon themselves. From here it is but a short step to assuming that any mother of a handicapped child could have avoided her situation had she so chosen. Such views are encouraged by irresponsible statements by people who should know better, such as 'we have the technology and the skill to detect almost all serious abnormalities in the early stages of pregnancy' (Toynbee 1981).

The existence of fetal diagnosis has opened doors that cannot be closed again. Pregnancy will never be the same, even for mothers who decline to take part, because they will always know that they could have had that knowledge and could have acted on it. The social pressures to participate in screening programmes and to terminate an affected pregnancy are considerable. Women may, as a result, experience considerable stress and find themselves acting against their own moral convictions. This is not to say that most women do not want the reassurances that fetal diagnosis can give. Most do, but the pressures, dilemmas and anxieties are real and should be recognized. Participation in screening programmes must be the choice of the individuals concerned, a choice which must be based on appropriate information and must be respected and supported by health professionals.

This commentary is based on a monograph entitled 'Calming or Harming? A critical review of psychological effects of fetal diagnosis on pregnant women' by Josephine M. Green. Available from the Galton Institute, 19 Northfields Prospect, Northfields, London SW18 1PE, Price £5 incl. p&p.

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Fish-oil and pre-eclampsia

Cod and halibut liver oil have been used for generations as a daily supplement of vitamin A and D. During World War II, the Minister of Food in the UK established a scheme for free distribution of fish-oil to all infants up to 5 years of age and pregnant and nursing women. The administration of fish-oil to children was widespread until the late 1950s and many people must still remember the characteristic fish-oil flavoured hiccups of their childhood The current scientific interest in the health effects of fish-oil was inspired by the studies undertaken in the 1970s among Greenland Eskimos, who have a low mortality from heart disease and a high consumption of sea mammals and fish (Dyerberg *et al.* 1978; Bjerregaard & Dyerberg 1988). For a long time fish-oil research focused primarily on aspects related to the pathogenesis of ischaemic heart disease. A large number of diseases have been considered to be preventable or curable by fish-oil (Gibson 1988) but only recently has it been suggested that fish-oil supplements might lessen the occurrence of obstetric complications such as preterm delivery (Olsen *et al.* 1986) and pre-eclampsia (Dyerberg & Bang 1985; Romero *et al.* 1988), and that it may increase fetal growth (Olsen *et al.* 1990).

The beneficial effect of fish-oil seems to be associated mainly with its long chain n-3 fatty acids, eicosapentaenoic (EPA), docosapentaenoic (DPA) and docosahexaenoic (DHA) acids. These belong to the n-3 polyunsaturated fatty acids which, together with the n-6 fatty acids derived primarily from vegetables, represent the main polyunsaturated fatty acids in our diet. The n-number indicates the location of the first double-bond counting from the methyl-end of the fatty acid. The n-3 fatty acids are synthesized by algae and phytoplankton and progress up the food chain until they are transferred by fish and other sea-foods to humans. Large amounts of the long chain n-3 fatty acids are present in the phospholipids in the human retina and brain, and there is growing evidence that they are essential to the development of the fetal brain (Neuringer *et al.* 1988). For this reason alone, they may be of great importance in the diet of pregnant women.

Gestational hypertension is associated with vasoconstriction and endothelial damage (Pritchard *et al.* 1976; Wardle & Menon 1969). The damage to the endothelium may cause thrombocyte aggregation and activation of the coagulation cascade. The thrombocyte aggregation leads to release of thromboxane A_2 and serotonin, resulting in further vasospasm, thrombocyte aggregation, and endothelial injury. Arachidonic acid, an n-6 fatty acid, is the precursor of thromboxane A_2 (TXA_2), which is synthesized in platelets, and prostacyclin I_2 (PGI_2), which is produced in endothelial cells. TXA_2 causes platelet aggregation and vasoconstriction, whereas prostacyclin has the opposite effect (Oates *et al.* 1988). Gestational hypertension is associated with a decrease in prostacyclin synthesis (Ylikorkala & Makila 1985), and an increase in TXA_2 synthesis (Fitzgerald *et al.* 1990). This probably contributes to the increased thrombocyte aggregation and vasoconstriction seen in this disease (Walsh 1985). It has been shown that low-dose aspirin can suppress the production of TXA_2 by inhibition of platelet cyclooxygenase, whereas the production of prostacyclin remains unchanged (Schiff *et al.* 1989, Benigni *et al.* 1989). Reduction in thrombocyte aggregation, vasospasm, endothelial damage and thrombosis associated with pre-eclampsia may be the mechanism behind the reduced occurrence of pregnancy-induced hypertension seen in controlled studies with low dose aspirin (Beaufils *et al* 1985; Wallenburg *et al.* 1986).

A change in haemostatic balance towards increased vasodilatation and decreased thrombocyte aggregation is also found after intake of long chain n-3 fatty acids (Goodnight 1989; Leaf & Weber 1988). Like arachidonic acid, eicosapentaenoic acid acts as a substrate for the cyclooxygenase enzyme producing the precursor of TXA_3, which is less active physiologically than TXA_2, and PGI_3, which is equipotent with its arachidonic acid-derived counter-part, PGI_2. As measured by urinary metabolites, n-3 fatty acid supplementation inhibits the production of TXA_2 and increases that of PGI_3, while it leaves PGI_2 largely unaffected. The result of these effects is a shift in the balance towards reduced platelet aggregation and increased vasodilation. For these reasons dietary supplementation with cod-liver oil has been suggested as an alternative to aspirin administration for the prevention of gestational hypertension (Romero *et al.* 1988). However, n-3 fatty acids have other haemato-vascular effects (Goodnight 1989; Leaf & Weber 1988) that may have therapeutic or prophylactic value in gestational hypertension. Intake of n-3 fatty acids reduces the viscosity of the blood, partly by reducing plasma viscosity, and partly by increasing deformability of the erythrocytes. A moderate reduction in arterial blood pressure is seen in normotensive subjects as well as in those with mild hypertension. After intake of fish-oil, the vasospastic response to catecholamines and angiotensin II is reduced, a response which is normally increased in pre-eclampsia. Moreover, docosahexaenoic acid in the blood platelets seems to inhibit thrombocyte aggregation by means other than the effect on eicosanoid metabolism. Also, endogenous fibrinolytic activity is increased as tissue plasminogen activity increases and inhibitors of plasminogen activators are reduced. Thus, contrary to low-dose aspirin, which seems specifically to block the thrombocyte production of TXA_2, the n-3 fatty acids may block the atherosclerotic process at several different levels, although the doses needed to obtain the effects mentioned are disputed, and may be quite substantial. These potential anti-atheromatic effects of n-3 fatty acids may also be important in the prevention and treatment of pre-eclampsia because many of the same processes, similar to those seen in atherosclerosis, occur in the placenta (Robertson *et al.* 1975; Sheppard & Bonnar 1976).

The possible preventive effect of fish-oil in pre-eclampsia is supported indirectly by the controlled study undertaken by the People's League of Health (1946) during 1938–39 in London and which has been reviewed recently by Olsen & Secher (1990). More than 5000 pregnant women were allocated alternately to treatment with a dietary supplement containing vitamins, minerals and halibut liver oil, or to no treatment; the halibut liver oil contained a comparatively low dose of n-3 fatty acids (about 0·1 g per day). The group receiving the supplement had less toxaemia than the control group. No firm conclusions can be drawn as to which components of the treatment caused the effects seen, but it is striking that among the controlled studies undertaken later with minerals and vitamins given in amounts comparable to those given in this trial, none demonstrated convincing effects on pre-eclampsia, and none employed n-3 fatty acids as part of the treatment.

Like any other therapy, fish-oil supplementation is associated with side effects. By far the most frequently reported is belching and unpleasant taste, but this is trivial compared to the risks posed by full-blown pre-eclampsia. More serious is the theoretical possibility of an increase bleeding tendency expected from the inhibitory effects of n-3 fatty acids on platelet aggregation, vasoconstriction, and certain stages in the coagulation cascade. Such adverse effects have not, to our knowledge, been reported in any of the large number of fish-oil supplementation studies published, but none of these studies involved pregnant women and pregnancy may pose special problems. Aspirin and other prostaglandin synthesis inhibitors and n-3 fatty acids have, as already mentioned, some similarity in their actions on coagulation. It is therefore reassuring that none of the controlled trials of aspirin have reported any complications that could be ascribed to an increased bleeding tendency, moreover multicentre trials of low-dose aspirin have obtained ethical approval in the UK and the USA. Another possible concern is that the highly unsaturated n-3 fatty acids are easily oxidized, producing substances that may carry health risks (Sanders 1989); however, these products are kept at a minimum in most of the fish-oil preparations on the market, and the use of gelatine capsules and the addition of natural antioxidants to the preparations provide protection against further oxidation. Nevertheless, because of the small possibility of side effects, studies of fish-oil supplements in pregnancy should be carefully designed in order to monitor any deleterious effects on mother or child.

There has been public interest in the protective effects of fish-oil for several years in relation to cardiovascular and other diseases. It may only be a question of time until the possibility of beneficial effects in pregnancy will have resulted in such widespread use that it will be very difficult to investigate the effects of this easily accessible food supplement. Large controlled multicentre trials should be organized as soon as possible to assess any beneficial or negative effects of fish-oil supplementation in pregnancy. Such a multicentre study is currently being organized from our clinic in which investigators are invited to cooperate.

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In the commentary we have preferred to refer to reviews rather than original papers in order to reduce the number of references.

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Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis

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Abstract

Objective—To reexamine the mortality experience of a cohort of long-term users of hormone replacement therapy (HRT) in comparison with that reported previously for the same cohort of women, paying particular attention to cardiovascular mortality, deaths from breast and endometrial cancer, and deaths attributed to suicide or suspected suicide.

Design—Longitudinal cohort of 4544 long-term users of HRT amongst whom mortality is being monitored prospectively in comparison with expected rates in the female population of England and Wales (taking account of age and calendar period).

Subjects—4544 women, all of whom were recruited from specialist menopause clinics around Britain and had taken at least one year's continuous HRT at the time of recruitment to the study.

Main outcome measures—All cause mortality, cardiovascular mortality, deaths from female cancers, deaths attributed to suicide or suspected suicide.

Results—Overall mortality (based on 236 deaths over the entire study period from recruitment to December 1988) remained significantly lower than expected on the basis of national rates (relative risk (RR) 0·56, 95% confidence limits (CL) 0·47–0·66). When specific causes were considered, the only mortality ratios greater than unity were for injury, poisoning and violence (1·54, 95% CL 1·02–2·06), and for suicide and suspected suicide ('suicide') (2·40, 95% CL 1·68–3·11). Comparison of the ratios for the 112 additional deaths with those obtained in our previous analysis revealed that one of the few ratios to show any increase was that for breast cancer mortality. This rose from a significant deficit of 0·55 (95% CL 0·28–0·96) in the earlier period to 1·00 (95% CL 0·55–1·45) in the later period. There was also a suggestion of an increase in breast cancer risk with increasing duration since first use of HRT. Most of the other cause-specific ratios were very similar over the two periods. The ratio of death from all circulatory diseases was notably lower in the later analysis (RR 0·37, 95% CL 0·15–0·58) than in the earlier analysis (0·51, 95% CL 0·36–0·69), as were all of the subcategories of cardiovascular death. The mortality ratio for cancer of the ovary and uterine adnexa fell from 1·12 in the previous analysis to 0·63 (95% CL 0–1·41). The mortality ratio for 'suicide' also decreased, but was only slightly lower in the later period. As before, however, there was evidence of a relatively high prevalence of prior psychiatric problems amongst the recent 'suicide' deaths, suggesting that the excess of deaths from 'suicide' may be a mani-

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festation of selection.

Conclusion—These data are consistent with a beneficial effect of HRT on cardiovascular diseases, although updated information comparing progestogen-opposed and -unopposed treatment is not available. The increase in breast cancer mortality contrasts with the pattern for all other specific causes examined; taken together with the suggestion of an increase in breast cancer mortality with increasing interval since first exposure to HRT, this finding is somewhat worrying.

In 1987 we reported preliminary results on mortality and cancer incidence in our cohort of long-term users of hormone replacement therapy (HRT) in Britain. At that time we pointed to some of the study's limitations (i.e its relatively small size and therefore low power, the selected nature of the population, and the absence of an internal control group), most of which were a consequence of the low levels of long-term HRT use in Britain (Hunt *et al.* 1987). We were struck then by the generally low level of the mortality ratios, that for suicide and suspected suicide being a notable exception. We speculated about the mechanisms, including selection (an artefact which should have decreasing effect with increasing periods of follow-up), which might have contributed to such a deficit. It is now over 4 years since our last analysis (which considered all deaths to 30 June 1984) and the cumulative total of deaths has almost doubled to 236. During this period HRT has continued to attract considerable interest in both medical and lay circles, and use of the treatment has increased substantially. For these reasons a reanalysis of the mortality experience of the cohort seemed valuable.

Subjects and methods

A detailed description of the background to the study and of the characteristics of the women included has been reported elsewhere (Hunt *et al.* 1987). In brief, the 4544 women in the cohort were recruited from 21 menopause clinics around Britain; all had received at least 1 year's continuous treatment with HRT before recruitment. At the recruitment interview, each woman was asked about her obstetric, gynaecological and past medical history. Information was also recorded about some social and physical characteristics (including height, weight, blood pressure, marital status, occupation of self and spouse (if appropriate) and smoking history). A detailed HRT history was recorded up to the date of recruitment. Study participants were 'flagged' at the National Health Service Central Registries (NHSCRs) in Southport and Edinburgh, so that any deaths within the cohort are automatically notified to the authors.

Most of the 4544 women were aged between 45 and 54 years at their first use of HRT (63%) and at recruitment to the study (60%). Around 6% had never been married and nearly 20% were nulliparous. The women are known to be atypical of the general population in two respects. First, a relatively high percentage (36%) had had a hysterectomy at recruitment, some 2–2·5 times the proportion in the British population (Alderson & Donnan 1978); this is not surprising as hysterectomy (particularly when combined with bilateral oophorectomy) is often seen as an indication for therapy. Secondly, the women tended to be of a higher social class than women in general: roughly twice as many (46%) were classified as being in social classes I and II (using the Registrar General's classification (OPCS, 1980) and the occupation of the husband for married women to enable comparison with census figures) as would have been expected from general population figures.

One feature of the cohort which distinguishes it from most other populations of HRT users that have been studied is the variety of HRT preparations prescribed, and the relatively frequent use of 'opposed' oestrogens (i.e. oestrogens with added progestogens) amongst women who had not had their uteri surgically removed (Hunt *et al.* 1987). Treatment details were recorded at the time of recruitment, and were updated using a postal questionnaire which was administered in 1983. An analysis of the treatments used up to that time amongst a subset of 3198 women showed that mean duration of use of HRT was 66·9 months and 59% indicated that they were still using HRT. Women with intact uteri had experienced 21·3 months of unopposed use and 39·2 months of opposed use on average (Hunt *et al.* 1987). Corresponding figures for women who had undergone hysterectomy retaining at least one ovary were 52·6 months for unopposed use and 12·8 months for opposed use. Women who had had a hysterectomy with bilateral oophorectomy tended to have used therapy for the longest durations; their average duration of unopposed and opposed use was 66·4 and 8·6 months respectively. More recent information on HRT use is not available since the only data currently being collected are those provided by the NHSCRs.

The current analysis of mortality was conducted using the MANYEARS FORTRAN program (Coleman *et al.* 1986) and age-specific death-rates (for 13 quinquennial age groups from 20 to 84) for England and Wales for the calendar periods 1966–70, 1971–75, 1976–80 and 1981–85. The latter set of rates was also used to calculate expected mortality rates for 1986 to 1988. As in our previous analysis of mortality, women left the analysis when they died, reached the age of 85 or (in some analyses) when they had their uterus removed, but were not censored for any other reason. The closing date for analysis was set at 31 December 1988, to ensure sufficient allowance for complete ascertainment of deaths for the whole study period. All deaths were coded to the 9th revision of the International Classification of Diseases. In describing the mortality experience of the cohort in the results and discussion sections which follow, 'relative risk' and 'mortality ratio' are used interchangeably.

Results

Considering first the complete study period from recruitment to December 1988 (Table 1), the overall mortality in the cohort was significantly low (relative risk (RR) 0·56, 95% confidence limits (CL) 0·47–0·66). As in our previous analysis most of the cause-specific ratios were also low; the only ratios greater than unity in this analysis being for injury, poisoning and violence (RR 1·54, 95% CL 1·02–2·06), and for suicide and suspected suicide (RR 2·40, 95% CL 1·68–3·11). Most of the cause-specific mortality ratios for the complete study period were very similar to (and lower than) those reported previously. The only notable exception is the breast cancer mortality ratio which increased from 0·55 in our previous analysis to 0·76 in the overall analysis. The mortality ratios for ischaemic heart disease (RR 0·41, 95% CL 0·20–0·61) and all circulatory diseases (RR 0·44, 95% CL 0·28–0·59) were again significantly lower than expected, and a little lower still than previously reported. The ratio for cerebrovascular disease also decreased, from a non-significant deficit (RR 0·65) to a significantly decreased risk of 0·54 (95% CL 0·24–0·84).

A comparison of the earlier mortality experience (Hunt *et al.* 1987) with that in the 4·5 years since our previous analysis (Table 2) shows some interesting features. Mortality ratios for ischaemic heart disease, cerebrovascular disease, other circulatory disease and all circulatory disease are all lower in the later period, and that for cerebrovascular disease is now significantly less than unity. The mortality ratio has also decreased for all deaths due to injury, poisoning and violence. However, most of this decrease is accounted for by a decrease in 'other violence', whilst the deaths attributable to suicide or suspected suicide have changed very little, and the ratio remains significantly elevated. The ratio for ovarian cancer has decreased quite substantially, whilst the ratios for other neoplasms and all neoplasms have *increased* a little. It is noteworthy that, despite the elevated risk for *incident* endometrial cancers which we reported previously (Hunt *et al.* 1987), no deaths attributable to cancer of the endometrium had occurred before the closing date for analysis (December 1988); one death from endometrial cancer in February 1989 will appear in future analyses.

The overall all-cause mortality and that for 'all other causes' remain virtually unchanged. An analysis of all-cause mortality by interval since first exposure to HRT (risk interval) showed no indication of changing risk as the period since first exposure lengthened (relative risks are 0·53 for 0–4 years since first use of HRT, 0·60 for 5–9 years, 0·54 for 10–14 years since first use, and 0·55 for 15 or more years since first use).

The increase between the two periods in the breast cancer mortality ratios is in clear contrast to other causes of death, the relative risk almost doubling to 1·00 for the later period. There was a suggestion of an increased risk for breast cancer mortality with increasing interval since first exposure (Table 3) with ratios rising from 0·38 in the 0–4 years since first exposure group, through 0·74 for those first exposed 5 to 9 years pre-

Table 1. Mortality in the cohort by cause of death (up to December 1988)

	Number of deaths			
Cause of death (ICD 9th revision)	Observed (O)	Expected (E)	Ratio (O/E)	95% CL
Ca breast (174)	31	40·97	0·76	0·45–1·06
Ca endometrium including uterus unspecified (182; 179)	0	4·05 (2·70)*	–	0·00–0·97
Ca cervix (180)	2	6·80*	0·29*	0·00–1·05
Ca ovary and uterine adnexa (183)	12	13·46*	0·89*	0·36–1·43
Other neoplasms	71	100·85	0·70	0·51–0·90
All neoplasms (140–239)	116	166·13	0·70	0·55–0·85
Ischaemic heart disease	36	88·78	0·41	0·20–0·61
Cerebrovascular disease (430–438; 290·4)	23	42·34	0·54	0·24–0 84
Other circulatory disease	11	29·35	0·37	0·01–0·74
All circulatory disease	70	160·47	0·44	0·28–0·59
Suicide and suspected suicide	18	7·51	2·40	1·68–3·11
Other violent death	4	6·79	0·84	0·00–1·34
All deaths due to injury poisoning and violence (800–998)	22	14·30	1·54	1·02–2·06
Other causes	28	78·13	0·36	0·14–0·58
All causes	236	419·03	0·56	0·47–0·66

*Taking account of uterine status.
Ca, carcinoma; CL confidence limits.

viously, to 0·97 amongst those who were first exposed to HRT more than 10 years previously. However, this trend was not statistically significant (χ^2 for trend = 2·41; NS). An analysis of breast cancer mortality by calendar period showed no discernible trends, although the numbers were very small in some of the subgroups; the ratios were 0·00 (O/E = 0/0·21), 0·79 (1/1·26), 0·37 (3/8·05), 0·91 (17/18·60) and 0·78 (10/12·85) for the periods 1961–1970, 1971–1975, 1976–1980, 1981–1985 and 1986–1988 respectively.

We also analysed the mortality data by uterine and ovarian status at recruitment to the study, as we had previously observed much higher relative risks for breast cancer *incidence* amongst women who had had a hysterectomy with conservation of at least one ovary (3·08), than amongst those women who had had both ovaries removed at hysterectomy (1·66) and those who had retained their uteri (1·19) (Hunt *et al.* 1987). This pattern is not replicated for breast cancer *mortality*: the relative risks (considered over the entire study period from recruitment to December 1988) were 0·74, 0·82 and 0·74 respectively for these three ovarian/uterine status groups. In the previous analysis of breast cancer morbidity we also conducted a case-control analysis to compare the duration and type of treatment used by cases and non-cases. Unfortunately, the lack of recent data on use of treatment prohibited a similar analysis to see if the increase in breast cancer mortality was concentrated within users of particular types of oestrogens, notably ethinyl oestradiol as we had found previously for the incident cases (Hunt *et al.* 1987), or to examine breast cancer risk by duration of use.

Discussion

The current analysis showed that the recent mortality ratios were generally similar to (and usually lower than) those reported previously. The only notable exception to this general pattern is for breast cancer mortality which has

Table 2. Mortality in the cohort by cause of death, July 1984–December 1988

	Number of deaths			
Cause of death (ICD 9th revision)	Observed (O)	Expected (E)	Ratio (O/E)	95% CL
Ca breast (174)	19	19·05	1·00	0·55–1·45
Ca endometrium including uterus unspecified (182; 179)	0	1·99 (1.31)*	–	0·00–1·38 (0–1·71)*
Ca cervix (180)	0	2·93*	–	0·00–1·15
Ca ovary and uterine adnexa (183)	4	6·33	0·63	0·00–1·41
Other neoplasms	37	51·27	0·72	0·45–1·00
All neoplasms (140–239)	60	81·57	0·74	0·52–0·95
Ischaemic heart disease	16	46·74	0·34	0·06–0·63
Cerebrovascular disease (430–438; 290·4)	9	20·70	0·43	0·00–0·87
Other circulatory disease	5	14·54	0·34	0·00–0·86
All circulatory disease	30	81·98	0·37	0·15–0·58
Suicide and suspected suicide	7	3·17	2·21	1·11–3·31
Other violent death	1	3·06	0·33	0·00–1·45
All deaths due to injury poisoning and violence (800–998)	8	6·23	1·28	0·50–2·07
Other causes	14	36·75	0·38	0·06–0·70
All causes	112	206·53	0·54	0·41–0·68

*Taking account of uterine status.

increased quite substantially. In our previous report, we suggested that a plausible interpretation for the significantly elevated *incidence* of breast cancer observed in the face of significantly low *mortality* from breast cancer was that women with clinically recognisable breast cancer and those at high risk of the disease had been deemed not to be suitable candidates for long-term HRT, and had therefore been selected out of the cohort. In such circumstances, one might also have expected a low incidence of the disease, as well as low mortality, if HRT had no harmful effects (Hunt *et al.* 1987). As this was *not* what we observed, we suggested that breast cancer mortality would rise 'in due course'. It is of considerable interest that such a rise is already apparent. This is slightly worrying since we judged that a small part of the elevated incidence seen might have been attributable to diagnostic surveillance bias as the staging distribution of

Table 3. Breast cancer mortality in the cohort by interval since first exposure to HRT

	Number of deaths (breast cancer)			
Years since first exposure to HRT	Observed (O)	Expected (E)	Ratio (O/E)	95% CL
0–4	3	7·94	0·38	0·00–1·07
5–9	13	17·60	0·74	0·27–1·21
10+	15	15·43	0·97	0·47–1·47
Total	31	40·97	0·76	0·45–1·06

χ^2 for trend = 2·41 (NS)
HRT, hormone replacement therapy, CL, confidence limits

the incident tumours was relatively favourable. Of the 19 additional breast cancer deaths which have occurred since our previous analysis, 11 were known to us as incident cases at that time. The suggestion that breast cancer mortality may increase with increasing interval since first exposure to HRT is consistent with an adverse effect of HRT on breast cancer which has taken some time to manifest itself in a basically low-risk (selected) population. It is important to emphasize, of course, that the women in the cohort tend to be from higher social classes and therefore to be at a slightly increased risk of breast cancer.

Few data are available in the published studies on HRT and breast cancer *mortality*. On the whole, the studies of HRT and breast cancer *morbidity* do not provide evidence of an overall increase in breast cancer in women taking HRT (Hunt & Vessey 1990) However, there is some concern that women who take HRT for long periods may be at increased risk. Thus, it is noteworthy that (i) one of the largest and best-conducted case-control studies of HRT and breast cancer *morbidity* showed a statistically significant trend for increased risk with long durations of use (RR 1·0 overall, rising to 1·5 for 20 or more years of use) (Brinton *et al.* 1986); (ii) some increased risk of incident breast cancer with duration of use has been reported in four cohort studies of HRT (Hoover *et al.* 1976; Buring *et al.* 1987; Bergkvist *et al.* 1989; Mills *et al.* 1989), as well as our own (Hunt *et al.* 1987).

The association between unopposed use of HRT and endometrial cancer incidence is clearly established and widely replicated. It is worth emphasizing that although there is a significantly elevated incidence of this disease in the cohort (RR 2·84) (Hunt *et al.* 1987), no endometrial cancer deaths occurred in the cohort up to the end of study date, although three or four would have been expected on the basis of national rates.

There is considerable evidence to suggest that use of HRT may be protective against cardiovascular disease, although there is still concern that some of the apparent protective effect may be due to selection, and that the use of *opposed* therapy may not confer this benefit (Vessey & Hunt 1988). Five cohort studies, in addition to our own, have recently considered the relation between HRT and cardiovascular mortality (Stampfer *et al.* 1985; Wilson *et al.* 1985; Pettiti *et al.* 1986; Henderson *et al.* 1986; Bush *et al.* 1987). All of these were conducted in the United States and thus relate largely to the use of unopposed oestrogens (and principally to conjugated oestrogens). All but one provide evidence of some protection from cardiovascular mortality (the Framingham Study by Wilson *et al.* (1985) being an important exception) (see Hunt & Vessey 1989), as does a well-conducted case-control study of HRT and death from ischaemic heart disease (Ross *et al.* 1981).

In our previous report, we considered the possibility that the significant deficit of all deaths, and of cardiovascular deaths, that was observed could be attributable to a direct effect of the therapy or to the impact of selection (particularly since low mortality was seen across virtually all of the causes considered). We suggested that if the deficit had been concentrated within cardiovascular disease, the biological plausibility of the results would be enhanced. In this context the consistent *fall* in the mortality ratios for cardiovascular deaths, when comparing the later period of the study with the earlier results, perhaps points more to an effect of the therapy than to selection. Unfortunately, no data are available on recent use of HRT, so we are unable to see whether there is any difference in cardiovascular mortality for those women who have taken unopposed or opposed therapy. In our previous analysis, we considered the use of opposed therapy amongst the women with intact uteri who had died of ischaemic heart disease and found no evidence of a detrimental effect. The numbers were small, and would not allow us to make adjustments for the effects of uterine and ovarian status. However, given that women in the cohort have used opposed therapy more widely than in other studies of HRT reported to date, it is encouraging that we continue to observe a significant deficit of cardiovascular deaths in line with other studies.

The analysis of recent mortality has again shown a significantly elevated ratio for suicide and suspected suicide ('suicide'). In our previous report (Hunt *et al.* 1987) we recorded the fact that 7 of the 11 women whose deaths were attributed to 'suicide' had a history of psychiatric illness before their first use of HRT. We speculated that this too may reflect a selective process whereby some women with severe or intractable psychological problems were among those referred to menopause clinics. Four of the seven recent deaths due to 'suicide' occurred amongst women who had been recorded as having prior psychiatric problems at recruitment to the study, a prevalence over four times greater than that for the cohort as a whole (13%). This lends some support to our earlier conclusion that the excess of deaths from 'suicide' may be a manifestation of selection, although we are concerned that the reduction in the magnitude of the ratio (comparing the recent analysis with the previous one) is so small.

In summary, therefore, the data on all-cause mortality and particularly cardiovascular mortality continue to be reassuring. However, the fact that the breast cancer mortality ratio has increased and that the ratio for suicide and suspected suicide remains significantly elevated continue to raise some questions about the long-term effects of HRT.

Acknowledgments

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Five years with continuous combined oestrogen/progestogen therapy. Effects on calcium metabolism, lipoproteins, and bleeding pattern

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Abstract

Objective—To study the effect of long-term continuous combined oestrogen/progestogen therapy on calcium metabolism, lipoproteins, and bleeding pattern in early postmenopausal women.

Design—A prospective, open, controlled study. After initial examinations, control examinations were performed every three months for the first two years and every year for the following three (two) years, with determinations of bone mass, serum lipoproteins, and bleeding pattern.

Setting—Out-patient research clinic at The Department of Clinical Chemistry, Glostrup Hospital, Denmark.

Participants—Eighteen healthy women between 6 months and 3 years after a natural menopause, entered in a trial of continuous long-term hormone replacement therapy and a comparison group of 19 age-matched untreated women.

Intervention—The treated group received 2 mg of 17β-oestradiol combined with 1 mg of norethisterone acetate orally each day continuously for 5 years with a 3 month therapy-free interval after the first 2 years. The women were investigated before treatment, then every 3 months for the first 2 years and every year for the next 3 years for determinations of bone mass, serum lipoproteins and bleeding patterns. The comparison group was followed-up in parallel for the first 4 years. Forearm bone mass was measured with single photon absorptiometry. Blood and urine samples were taken in the morning after an overnight fast and tobacco abstinence.

Main outcome measures—The effects of hormone therapy on bone mineral content in the forearm, on serum and urine indices of calcium metabolism, on serum levels of total, high (HDL-C) and low (LDL-C) density lipoprotein cholesterol, and bleeding pattern.

Results—Bone mineral content in the forearm was stable during the 5 years of treatment, whereas it declined significantly averaging 10% after 4 years in the comparison group. The biochemical estimates of bone turnover decreased to premenopausal level in the hormone group, whereas they remained at a high level in the comparison group. In the hormone group total cholesterol and LDL-C decreased by 20% whereas HDL-C was virtually unchanged. The treatment was associated with minor irregular bleeding in nine women during the first 6 months of treatment, after which no bleeding was experienced.

Conclusion—Continuous combined oestrogen/progestogen therapy can keep early postmenopausal women free of bleeding episodes for a period of 5 years, after the first 6 months in which spotting occurs in 25% The therapy prevented bone loss completely. The changes in serum lipoproteins were concordant with a lipid profile associated with a decreased risk of coronary heart disease.

Postmenopausal hormone replacement therapy (HRT) is increasingly used for relief of climacteric symptoms or prevention of osteoporosis (Lindsay *et al.* 1976; Christiansen *et al.* 1981). To avoid increased risk of endometrial cancer, the oestrogen component should be combined with a progestogen (Whithead *et al.* 1981; Persson *et al.* 1989). Cyclical addition of a progestogen induces monthly menstrual bleeding, which

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many women consider inconvenient, and to avoid this bleeding, the continuous combined oestrogen/progestogen regimen was introduced (Mattson *et al.* 1982; Jensen *et al.* 1987). The rationale behind this treatment is that continuous progestogen stimulation will keep the endometrium atrophic. We and others have previously published the effect of 2 years continuous combined treatment with 2 mg oestradiol (E2) and 1 mg norethisterone acetate (NETA) on calcium metabolism (Riis *et al.* 1988; Munk-Jensen *et al.* 1988), lipoproteins, bleeding pattern (Jensen *et al.* 1987) and blood pressure (Hassager & Christiansen 1988), but no data have been reported on treatment for longer than 2 years. Lindsay *et al.* (1987) demonstrated that unopposed oestrogen has a lasting effect (16 years) in prevention of the postmenopausal bone loss, but recently Munk-Jensen *et al.* (1988) raised the question whether the preventive effect of combined oestrogen/progestogen therapy on bone loss will continue beyond a period of 2 years. In this paper we present data on calcium metabolism, lipoproteins, and bleeding pattern from a 5-year follow-up of a group of women treated with continuous combined oestrogen/progestogen hormonal replacement therapy.

Subjects and methods

The women entered a double-blind placebo controlled study in 1983 (Jensen *et al.* 1987; Riis *et al.* 1988; Hassager *et al.* 1988). They were all healthy and had had a natural menopause 6 months to 3 years previously. None was taking medication known to influence any of the studied variables. The 49 women in the study were allocated to 2 years treatment with either continuous combined oestrogen/progestogen therapy, 2 mg of 17β-oestradiol (E2) and 1 mg of norethisterone acetate (NETA), the HRT group (n=24), or a placebo (n=25). After 2 years, the treatment was withdrawn for 3 months and then resumed by the HRT group. The placebo group did not resume therapy, and did not continue in the trial. Data from a group of 19 untreated age-matched women, who were followed-up in parallel during the first 4 years of treatment, were included as the control group in this study. The initial data from the women who completed the study in the HRT group (n=18), the original placebo group (n=22) (Riis *et al.* 1988), and the control group are given in Table 1. The groups were comparable. We examined the women every 3 months during the first 2 years, and thereafter once every year.

Compliance

During the first year of treatment three women in the HRT group left the study one because of continuous irregular bleedings and the other two because of lack of time. No woman left the study in the second year. During the third year three women left because of lack of time, whereas no women left in the fourth and fifth year. This left 18 women completing all 5 treatment-years.

Bone mass measurements

Bone mineral content (BMC) in each forearm was measured by single photon absorptiometry with a ^{125}I source (100 mCi), with a photopeak at 27 keV. The method determines the BMC in the proximal (BMCprox) and distal (BMCdist) regions of the distal third of the forearm, which have estimated trabecular bone contents of 13% and 55%, respectively. The *in vivo* precision is 1% for the proximal region and 1.5% for the distal region (Nilas *et al.* 1985).

Biochemical measurements

Blood samples were taken and urine collected in the morning after an overnight fast and tobacco abstinence. All samples were stored at −20°C.

Plasma bone Gla protein (BGP) was determined by radioimmunoassay (Johansen *et al.* 1987). The antiserum was raised in rabbits immunized with purified intact calf BGP and homogeneous calf BGP was used for standard and tracer. The intra- and inter-assay variations were 7% and 12%, and the sensitivity was 0.8 µg/l. Serum total alkaline phosphatase (sAP) was measured enzymatically according to Scandinavian Recommendations. Serum phosphate was determined by a standard procedure of our laboratory. Fasting urinary calcium and creatinine were measured with a SMA 6/60 autoanalyser, and calcium excretion was corrected for creatinine excretion (FU Ca/Cr). Fasting urinary hydroxyproline was measured by a spectrophotometric method (Pødenphant *et al.* 1984) and corrected for creatinine excretion (FU Hpr/Cr).

Serum lipids and lipoproteins. The high density lipoprotein (HDL) fraction was separ-

Table 1 Comparison of the hormone, the original placebo, and the present control groups

	Hormones (n=18)	Placebo (n=22)	Controls (n=19)
Age (years)	50.5 (0·4)	49·9 (0·6)	50·9 (0·4)
Height (cm)	162 (1)	164 (1)	162 (1)
BMCprox (units)	37·1 (1·1)	39·7 (1·2)	38·0 (1·2)
BMCdist (units)	36·7 (1·4)	39·7 (1)	36·4 (1·4)
sAP (U/l)	167 (11)	165 (1)	176 (10)
pBGP (μg/l)	8·9 (0·9)	9·2 (1·0)	12·0 (1·2)
FU Hpr/Cr (mmol/mol)	12·1 (0·7)	12·3 (0·5)	14·0 (0·8)
s-Cholesterol (mmol/l)	6·8 (0·3)	6·2 (0·2)	6·4 (0·2)
s-LDL-C (mmol/l)	4·6 (0·3)	4·0 (0·2)	4·1 (0·2)
s-HDL-C (mmol/l)	1·7 (0·1)	1·7 (0·1)	1·8 (0·1)
Blood pressure (mmHg)			
Systolic	129 (3)	120 (3)	122 (3)
Diastolic	79 (2)	72 (1)	74 (2)

Results are mean (SEM) values.

Abbreviations: BMCprox =bone mineral content of the proximal part of the distal forearm; BMCdist=bone mineral content of the distal part of the distal forearm; sAP= serum alkaline phosphatase; pBGP= plasma bone GLA protein; FU Hpr/Cr= fasting urinary hydroxyproline/creatinine; s-LDL-C= serum low density lipoprotein cholesterol; s-HDL-C= serum high density lipoprotein cholesterol.

ated from chylomicrons and low density lipoprotein (LDL) by a phosphotungstate-MgCl$_2$ precipitation technique (Finley *et al.* 1987). Total serum cholesterol and HDL cholesterol were determined by an enzymatic technique with an LKB Ultrolab System. The intra- and inter-assay variations were 2% and 2%, (total serum cholesterol), respectively, and 3% and 6% (HDL cholesterol). Serum triglycerides were determined by an enzymatic technique with an LKB 8600 reaction rate analyser, and LDL cholesterol was then estimated as described by Friedewald *et al.* (1972).

Uterine bleeding

Episodes of bleeding were recorded on a daily questionnaire by each subject and produced at each examination.

Statistical analysis

One way analysis of variance was used to compare initial data. Student's t-test for paired and unpaired data was used to compare differences within and between groups.

Results

After 4 years treatment, the mean weight gain in the HRT group was 1·4 kg which was not statistically significant, whereas the control group had gained 2·8 kg ($P<0·01$). The baseline systolic and diastolic blood pressures did not differ significantly between the two groups. After 4 years treatment the blood pressure was unchanged in the HRT group but had risen in the control group, the increase in diastolic blood pressure was significant ($P<0·001$)

Figure 1 shows the BMC in the proximal and distal parts of the forearm. In the HRT group it was unchanged during the 5 years of treatment, whereas the control group showed a bone loss averaging 10% after 4 years ($P<0·001$). The difference between the two groups was highly significant. The 3 months of withdrawal of treatment had no detectable effect on the BMC. Figure 1 also shows the correlation between time

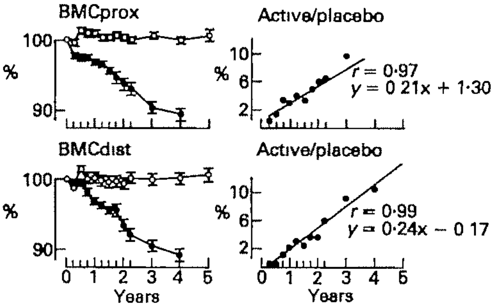

Fig. 1. Left. bone mineral content in the proximal (BMC prox) and distal (BMC dist) forearm during 5 years of continuous combined oestrogen/progestogen therapy (○), and 4 years without therapy (●). Right· correlation between time and active/'placebo' therapy.

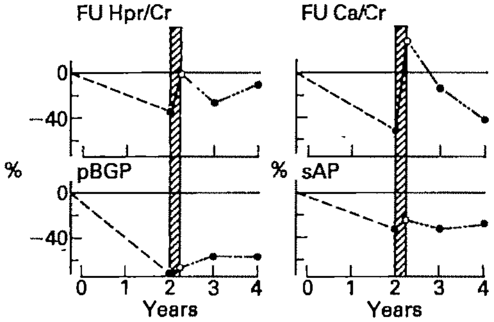

Fig. 2. Biochemical indices of bone turnover during 4 years of continuous combined oestrogen/progestogen therapy (●) and during 3 months of withdrawal (O). The values in the active drug group are corrected for the values in the control group. FU Hpr/Cr=fasting urinary hydroxyproline/creatinine; FU Ca/Cr=Fasting urinary calcium creatinine pBGP=plasma bone GLA protein; sAP=serum alkaline phosphatase.

and the active/placebo effect on BMCprox and BMCdist. The *r* values were 0·98–0.99 (P<0·001).

Figure 2 shows the biochemical indices of bone turnover in the HRT group corrected for the values in the control group. HRT depressed the indices both of bone resorption (FU Ca/Cr and FU Hpr/Cr) and of bone formation (sAP and pBGP) throughout the treatment period. Three months of treatment withdrawal resulted in significant increases in the indices of bone resorption, and reinstitution of therapy depressed them again. Withdrawal of treatment produced no detectable changes in the biochemical indices of bone formation (pBGP or sAP).

Figure 3 gives the individual percentage changes over 4 years in total cholesterol, LDL-C, and HDL-C in the two groups, and the mean values (%) of total cholesterol over the 5 years of treatment. HRT produced highly significant decreases in total cholesterol and LDL-C averaging about 20%. Withdrawal of treatment resulted in significant increases. The values were unchanged in the control group. HDL-C fluctuated during treatment and the fluctuations were parallel in the two groups during the first 2 years. However, withdrawal of treatment increased HDL-C (P<0·01), and in the fourth year there was a tendency to lower HDL-C values in the HRT group than in the control, the difference was not significant.

In all, eight women (including the one that left because of bleeding) had episodes of bleeding during the first 6 months of treatment, after which only one woman had a slight bleed in the second year of treatment. The bleeding was characterized as spotting. No biopsies showed proliferative endometrium.

Discussion

We have previously demonstrated that postmenopausal oestrogen/progestogen therapy prevents the gain in body weight and increase in the diastolic blood pressure that seem to take place after the menopause (Hassager & Christiansen 1988). The present study demonstrates that these effects are present also after 5 years of treatment.

There is still controversy as to whether oestrogen therapy has a lasting effect on the prevention of postmenopausal bone loss (Munk-Jensen *et al.* 1988). The present study shows that during 5 years of treatment with E2 continuously combined with NETA no escape-phenomenon appeared either in the bone mass or in the biochemical indices of bone turnover. We did not measure the bone mineral content in the spine in the present 5 years of follow-up. The postmenopausal oestrogen-dependent bone loss in the forearm parallels that in the spine as in all other parts of the skeleton (Riis & Christiansen 1988). The preventive effect of oestrogen therapy is accordingly present throughout the skeleton. This strongly indicates that the bone mass values shown in the present study are valid not only for the forearm, but also for the spine and indeed the whole skeleton.

Three months withdrawal of treatment produced significant increases in the indices of bone

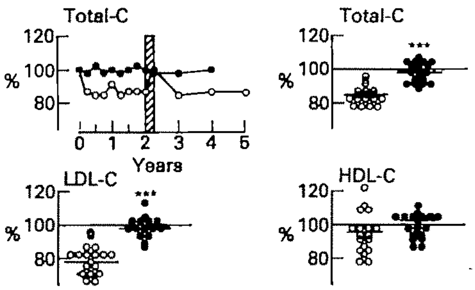

Fig. 3. Mean values of serum total cholesterol (total-C) over 5 years and individual changes over 4 years in total cholesterol, LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) in the group treated with oestrogen/progestogen (O) and in the group of controls (●). ***P<0·001 (difference between groups)

resorption but not those of bone formation. This is consistent with the fact that oestrogens primarily affect bone resorption, with a secondary and somewhat delayed effect on bone formation (Parfitt 1982). However, 3 months of withdrawal did not produce a detectable loss of bone. This indicates that the biochemical estimates of bone resorption are very sensitive to changes in the serum concentrations of oestrogen, and that a steady state has to be reached before the indices can be used to estimate the calcium balance (Christiansen *et al.* 1987). We have shown previously that a significant loss of bone is detectable as early as 6 months after withdrawal of treatment (Christiansen *et al.* 1981).

Derivatives of 19-nor-testosterone have been shown to affect adversely the beneficial oestrogenic effect on serum lipoproteins (Hirvonen *et al.* 1981; Tikkanen *et al.* 1982). We have previously shown (Jensen *et al.* 1987) that 2 years of treatment with small doses of NETA (1 mg) given sequentially or continuously with oestrogen cancels the increasing effect of oestrogen monotherapy on HDL-C, resulting in unchanged serum concentrations of HDL-C. On the other hand, the combination of E2 plus NETA, either sequentially or continuously, seems to produce a more pronounced decrease in total cholesterol and LDL-C than what would be expected with oestrogen monotherapy (Jensen *et al.* 1986). The present study demonstrates that these effects continue during 5 years of treatment. It also indicates that withdrawal of treatment brings about abrupt increases in total cholesterol and LDL-C. The increase in HDL-C following withdrawal indicates that the treatment does in fact depress HDL-C, but to such a small extent that it was impossible to detect the difference between the treatment and the control groups during the first 2 years treatment. This is supported by the fact that HDL-C was lower in the treatment group than in the control group during the third and fourth years of treatment, although the difference was not statistically significant. Epidemiological studies suggest that the decreased risk of coronary heart disease resulting from intervention (dietary or medical) is mainly due to a decrease in the LDL-C concentration and that a 1% decrease in LDL-C corresponds to a 2% decrease in coronary heart disease (Lipid Research Clinics Program 1984). The Consensus Conference (1985) stated that this has been demonstrated most conclusively in men, but that a body of evidence justifies the conclusion that similar protection will be afforded to women. In contrast, epidemiological studies of oestrogen replacement therapy have found the decreased risk of coronary heart disease following oestrogen monotherapy (conjugated equine oestrogen) is mainly associated with the increased serum concentrations of HDL-C (Bush *et al.* 1983, Bush *et al.* 1987). The most pronounced effect of conjugated equine oestrogens on serum lipoproteins is, however, the increase in HDL-C, whereas the other lipoproteins are affected to a much lesser extent (Lobo 1988). This may explain the controversy. The 20% decrease in LDL-C during the present treatment regimen suggests a possible 40% decrease in the risk of coronary heart disease.

Many women consider the cessation of periods to be an advantage of the menopause and they are reluctant to start oestrogen replacement therapy because of the withdrawal bleeds. The present study shows that with the correct oestrogen/progestogen combination it is possible to avoid regular withdrawal bleeds and to eliminate (almost) unpredictable spotting also in the long term.

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Effect on plasma lipids and lipoproteins of postmenopausal oestrogen therapy with added dydrogesterone

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Summary. In a prospective, randomized, cross-over study, 14 postmenopausal women completed 9 months of treatment with conjugated equine oestrogens, 1·25 mg daily. Seven women added dydrogesterone 20 mg daily for 12 days during months 2, 3 and 4, and then 10 mg daily for an identical time in months 5, 6 and 7. The other seven women added the two dydrogesterone doses in reverse sequence. No dydrogesterone was taken during months 8 and 9. Lipids and lipoproteins were measured before treatment and at the end of months 4, 7 and 9. Lipids were also estimated in an untreated (reference) group of eight postmenopausal women on two occasions 6 months apart; these showed significant changes in HDL_2- and HDL_3-cholesterol. In the treatment group, HDL-cholesterol and apolipoprotein (apo) A1 were significantly higher and LDL-cholesterol and apo B were significantly lower at months 4, 7 and 9 compared with baseline values. Triglyceride levels were increased significantly over baseline values, but remained within the normal range. No significant differences between the two dydrogesterone doses were observed on any lipid and lipoprotein fraction, nor were there any differences between the oestrogen-only and oestrogen/dydrogesterone treatment phases. Dydrogesterone appears to cause little, if any, lipid and lipoprotein changes and assessment in a larger population of postmenopausal women is warranted.

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The effect of loss of ovarian function on lipid and lipoprotein metabolism may contribute to the increase in arterial disease found in some postmenopausal women (Lobo 1987). High density lipoprotein (HDL) levels are inversely related to the incidence of coronary heart disease and they are relatively unchanged by the menopause, whereas there is an increase in the atherogenic low density lipoprotein (LDL), which contains approximately 70% of the circulating cholesterol (Marshall & Ballantyne 1986).

The effects of unopposed oral oestrogens on arterial disease risk and lipid and lipoprotein metabolism are beginning to be unravelled. All but two (Petitti *et al.* 1979; Wilson *et al.* 1985) of the published epidemiological studies (Hammond *et al.* 1979; Bush *et al.* 1983 & 1987; Stampfer *et al.* 1985; Ross *et al.* 1987) have reported that such treatment lowers arterial disease risk, and reductions of between 30% and 70% have been reported (Bush *et al.* 1983 & 1987; Ross *et al.* 1987). In studies of at least 3 months duration, subcutaneous and percutaneous routes of oestrogen administration have also been shown to increase HDL-cholesterol and to reduce LDL-cholesterol levels (Whitehead & Fraser 1987), and it has been argued that this is the mechanism through which oestrogens reduce arterial disease risk. Whilst lipid and lipoprotein changes are important, other effects of oestrogens on arterial health may have a role in the human (Sarrel 1988).

In women with a uterus, combined oestrogen/progestogen treatment has become standard practice because unopposed oestrogens increase the risk of endometrial hyperplasia (Whitehead *et al.* 1979) and cancer (Gambrell 1986; Peterson *et al.* 1987), and combined treatments prevent these abnormalities (Gambrell 1986; Whitehead & Fraser, 1987*a;* Persson *et al.* 1989). However, some progestogens have adverse effects on the HDL/LDL ratio (Silfverstolpe *et al.* 1979; Hirvonen *et al.* 1981), and there is a potential risk that combination therapy may diminish the cardiovascular benefits obtained with oestrogen-alone (Crona *et al.* 1986). Thus, the ideal progestogen for postmenopausal use should protect the endometrium but not reverse the beneficial lipoprotein changes observed with oestrogen-only therapy.

We have reported previously that dydrogesterone (Duphaston: Duphar Laboratories, Southampton) has the required endometrial effects (Lane *et al.* 1986). We have therefore determined the lipid and lipoprotein effects of two doses of dydrogesterone which are known to exert endometrial effects in postmenopausal women taking oestrogen.

Subjects and methods

We studied two groups of women: all had postmenopausal plasma gonadotrophin levels >20 IU/l. and none had received exogenous sex steroids in the previous 6 months. One group (treatment) was symptomatic and requesting hormone therapy; the second (reference) group was not.

Treatment consisted of conjugated equine oestrogen (Premarin: Wyeth/Ayerst Laboratories, Maidenhead) 1·25 mg daily for 9 months. At the end of the first month, eight of the 16 symptomatic women were randomly allocated to add dydrogesterone 20 mg daily for the first 12 days of months 2, 3 and 4, and then dydrogesterone 10 mg daily for the same time in months 5, 6 and 7 (Group 1). The other eight women received the two dydrogesterone doses in reverse sequence (Group 2). By including a placebo tablet, the dydrogesterone dose was administered in a double-blind fashion. The randomization schedule ensured even distribution of smokers and non-smokers into the two dydrogesterone dosage groups. In months 8 and 9, all women took only the conjugated equine oestrogens.

The reference group of eight women were matched for age (±2 years), weight, years since menopause and smoking habit to eight of the 16 treated women (four from each group). During the study, all women were asked to try to keep their weight, smoking habits and intake of alcohol and caffeine constant. Drugs known to influence lipid and lipoprotein metabolism were banned.

Blood sampling

In the treatment group blood samples were collected by venepuncture on five occasions, two before treatment to screen for pre-existing lipid abnormalities and to establish baseline values. (Two women had baseline lipid values outside the reference range for the laboratory and were excluded from the study.) Two further blood samples were obtained on day 10 of treatment months 4 and 7. The fifth sample (final assessment) was obtained after 2 months of oestrogen-

Table 1. Coefficients of variation

Coefficients of variation	Total Ch	Total Tg.	VLDL Ch.	VLDL Tg.	LDL Ch	HDL Ch.	HDL_2 Ch	Total apo A	Total apo B
Within batch (%)	0·43–0 9	0·99–1·53	5·16–6·0	3·62–7 55	0 97–1·02	0 66–1·59	9·0 –12·6	1·0 –1·49	1 5 –2·0
Between batch (%)	0·81–1 04	1·43–2·31	5·82–8·96	6 03–7·22	0·84–1·56	0 92–1 44	10·12–14·1	1·32–2·44	1·81–3·52

Ch. = cholesterol. Tg. = triglycerides

only therapy to determine whether removal of the dydrogesterone affected lipid and lipoprotein metabolism. Women in the reference group had blood samples taken on two occasions, 6 months apart.

Blood samples were collected after a 14-h overnight fast. The woman rested for 30 min and blood was taken with the patient sitting and without a tourniquet. Women who reported a recent febrile illness were given an extra month's supply of drugs and asked to return at the same time in the cycle the following month.

Lipid and lipoprotein analyses

A 10 ml volume of blood was added to 10 mg of sodium EDTA and after mixing gently was centrifuged at 4°C. The separated serum was transported on ice to the lipid laboratory within 4 h, and the samples were stored at 4°C and analysed for lipids within 48 hours. Samples for apo A1 and apo B were stored at −70°C. The collection, transport, storage and subsequent analysis of the lipid and lipoprotein fractions complied with standards of the United Kingdom Collaborative Lipid Research Group.

Individual lipids and lipoproteins were assayed as follows: VLDL was isolated by preparative ultracentrifugation at a background density of 1·006 kg/l (105 000 *g* for 16 h) in a Kontron 45·6 rotor and the cholesterol and triglyceride content were measured. HDL was isolated by selective precipitation of the apo B containing VLDL and LDL-lipoprotein using heparin-manganese chloride and the cholesterol content was measured as described by Warnick & Albers (1979). The HDL_2-subclass was separated from an aliquot of the post-precipitation HDL supernatant. This was performed by preparative ultracentrifugation at a background density of 1·125 kg/l at 280 000 *g* for 3 h in a Beckman airfuge with isolation of HDL in the supernatant, and the cholesterol content was measured. Total plasma cholesterol and triglycerides, and the cholesterol and triglyceride content of the lipoprotein fractions detailed above, were measured enzymatically using Boehringer-Mannheim reagents in the Roche-Cobas centrifugal analyser. High and low quality control samples (Precilip$_R$ E.L. and Precilip$_R$), were included with each batch. HDL_3-cholesterol was estimated by difference (HDL-cholesterol minus HDL_2-cholesterol); LDL-cholesterol was estimated by the difference between total cholesterol minus VLDL cholesterol and minus HDL cholesterol. Apo A1 and apo B were measured using the Cobas Bio centrifugal analyser by immunoturbidimetric assay at 340 mm (Orion Diagnostica) against standard reference material. The between batch and within batch coefficient of variation for this laboratory are shown in Table 1.

Weight, tobacco, alcohol and caffeine consumption were recorded at each visit.

Statistical analysis

The demographic data were analysed using Student's unpaired *t* test. The lipid and lipoprotein results from the four time periods in the treatment group [(i) the pre-treatment baseline (mean of the two assessments); (ii) after 4 and (iii) after 7 months of combined therapy, and (iv) after 2 months of oestrogen-alone treatment] were analysed using a 2-way analysis of variance with Minitab on an IBM 3090.

When determining the significance of the changes, we calculated the 5% least significant difference between the means for the various time periods. Initially the 4 month and 7 month data were analysed using a cross-over analysis (Hills & Armitage 1979) to compare the effects of the two dydrogesterone dose levels. Change in body mass index (weight/height^2) was included as a covariate.

Although the sample size was limited by the financial constraints and the complexity of the study, power calculations suggested that with a

Table 2. Demographic details of the treatment and reference groups

	Treatment Group		Reference Group	
	Group 1 (20 mg then 10 mg DYD) ($n = 7$)	Group 2 (10 mg then 20 mg DYD) ($n = 7$)	Group 1 ($n = 4$)	Group 2 ($n = 3$)
Age (years)	48·6 (6·6)	50·7 (3·3)	52·5 (3·1)	52·7 (4·0)
Time since LMP (months)	16·3 (10·1)	36·0 (49·5)	48·0 (48·2)	60·0 (36)
Body mass index	23·4 (1·4)	23·8 (2·7)	22·4 (2·2)	22·3 (0·2)

LMP = last menstrual period.
DYD = Dydrogesterone
Results are mean (SD) values.

sample size of 16 women there would be sufficient power (80%) to detect a 10% reduction in HDL-cholesterol, which was regarded as having probable clinical significance.

Results

Demographic data for the treatment and reference groups are shown in Table 2. There were no differences between the groups for age and body mass index but the time from the last menstrual period was significantly shorter in group 1 ($P<0·05$).

Seven of the eight women in group 1 completed the study, one woman failed to attend for unknown reasons, she did not respond to telephone calls and letters. Likewise, seven of the eight women in group 2 completed the study; one was excluded because of non-compliance. There were no significant changes in body weight, tobacco, alcohol and caffeine consumption, and smoking habit in any of these 14 women during the study.

Seven of the eight women in the reference group completed the study. One patient failed to attend at 6 months. The reason is unknown as she could not be contacted.

Lipids and lipoproteins

In the treatment group, all samples were assayed for lipids and all samples, but one, for tri-

Table 3. Mean plasma lipid, lipoprotein and triglyceride values in the treatment and reference groups

	Treatment group				5% least significant difference between means	Reference group	
	Mean baseline	Month 4	Month 7	Month 9		Baseline	Month 6
Total-Chol	6·19	5·92	5·85	5·91	0·40	6·75	6·79
LDL-Chol	4·21	3·58§	3·39§	3·64§	0·38	4·52	4·80
HDL-Chol	1·84	2·15§	2·21§	2·09§	0·17	1·98	1·77
HDL_2-Chol	0·48	0·56	0·43	0·52	0·12	0·29	0·42*
HDL_3-Chol	1·36	1·59§	1·78§	1·57§	0·19	1·69	1·36§
VLDL-Chol	0·15	0·19	0·25*	0·19	0·06	0·26	0·21
Total-TG	1·01	1·34§	1·58§	1·45§	0·22	1·22	1·32
VLDL-TG	0·43	0·49	0·71‡	0·62‡	0·17	0·57	0·62
ApoA1†	170·4	216·2 §	229·4 §	223·8 §	22·76	175·1	156·5
Apo B†	113·1	99·7 ‡	94·2 ‡	99·2 ‡	10·22	116·5	108·4

All units in mmol/l except † which is mg/dl
Significant differences compared with baseline:
* $P<0·05$; ‡ $P<0·01$; § $P<0·001$.
chol = cholesterol.
TG = triglyceride.

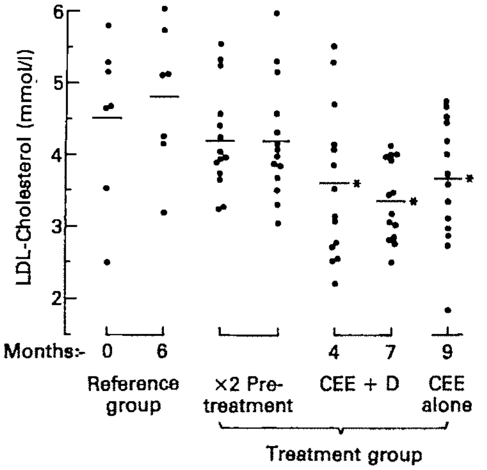

Fig. 1. LDL cholesterol values for the treatment and reference groups. CEE = conjugated equine oestrogens. D = dydrogesterone. *indicates statistically significant decrease ($P<0{\cdot}001$) compared with pretreatment.

glycerides; 14 samples were not assayed for apo A1 and apo B because too little plasma remained after thawing. In the reference group, one sample was not assayed for apo A1 and apo B for the same reason.

The results were analysed for an order (time) effect, and for a dose-response relation between the added dydrogesterone and lipid and lipoprotein changes. No order effect was observed in the treatment group irrespective of dydrogesterone sequence, and the analysis of variance on cross-over showed no significant differences between the two dydrogesterone doses; therefore, the data from the two dydrogesterone dose groups for each assessment (months 4 and 7) were pooled.

The results for the lipids, lipoproteins and apolipoproteins currently considered to be most important clinically are shown in Figs. 1–5. In each, the individual results for the treatment and reference groups are presented as scattergrams: the mean value at each assessment is indicated by a horizontal line. Unless otherwise stated, there were no significant changes with time in the treatment or reference groups. All the lipid, lipoprotein and triglyceride data are presented as means in Table 3 which also includes the statistical results.

Compared with pretreatment values, there were significant reductions in LDL-cholesterol ($P<0{\cdot}001$: Fig. 1) and apo B ($P<0{\cdot}01$: Fig. 2) at months 4, 7 and 9; there were no significant differences between these three assessments for the two lipid indices.

Compared with pretreatment values, there were significant increases in HDL-cholesterol ($P<0{\cdot}001$: Fig. 3) and apo A1 ($P<0{\cdot}001$: Fig. 4) at months 4, 7 and 9; there were no significant differences between these three assessments for the two lipid parameters.

Compared with pretreatment values, plasma total triglyceride was significantly increased ($P<0{\cdot}001$: Fig. 5), but the levels remained within the normal range for the laboratory.

During treatment there were no significant changes in plasma total cholesterol or HDL_2-

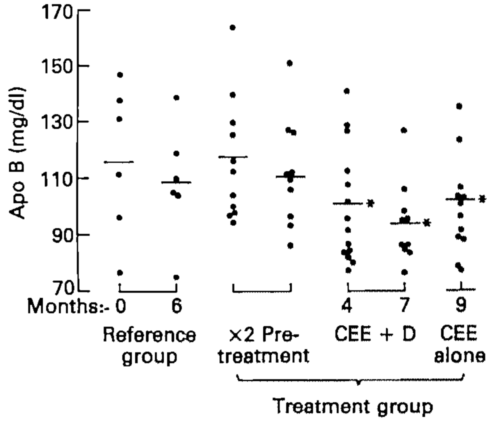

Fig. 2. Apo B values for the treatment and reference groups CEE = conjugated equine oestrogens D = dydrogesterone *indicates statistically significant decrease ($P<0{\cdot}01$) compared with pretreatment.

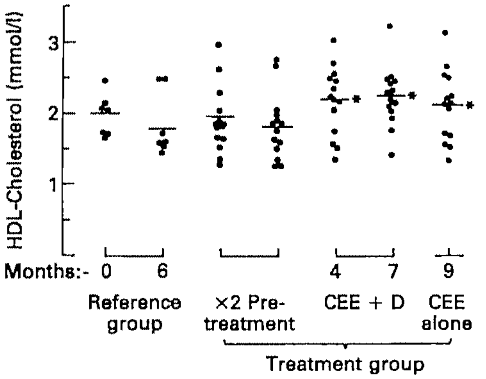

Fig. 3. HDL cholesterol values for the treatment and reference groups CEE = conjugated equine oestrogens. D = dydrogesterone. *indicates a statistically significant increase ($P<0{\cdot}001$) compared with pretreatment.

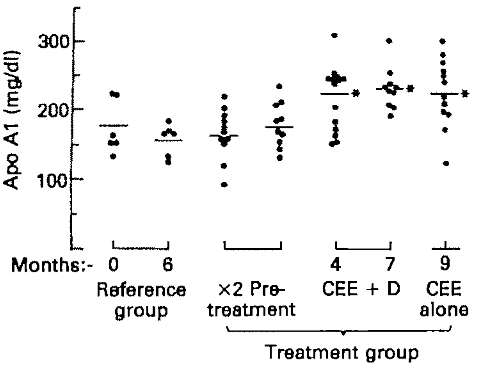

Fig. 4. Apo A1 values for the treatment and reference groups. CEE = conjugated equine oestrogens. D = dydrogesterone. *indicates a statistically significant increase ($P<0{\cdot}001$) compared with pretreatment.

cholesterol (Table 3). HDL_3-cholesterol was significantly ($P<0{\cdot}001$) increased: there were no significant differences between the two assessments during combined therapy and the values remained elevated after dydrogesterone withdrawal. VLDL-cholesterol was significantly increased ($P<0{\cdot}05$) at the second assessment during therapy (month 7). VLDL-triglyceride was also significantly increased at this time, and at the last oestrogen-only assessment ($P<0{\cdot}01$).

Compared with baseline values, HDL_2-cholesterol was significantly increased ($P<0{\cdot}05$) and HDL_3-cholesterol was significantly lower ($P<0{\cdot}001$) at the second, 6 month assessment in the reference group. No other significant changes were observed in this group (Table 3).

Discussion

Gynaecologists are increasingly aware of the metabolic consequences of endogenous and exogenous sex steroids. We assayed lipid and lipoprotein levels twice before treatment to exclude pre-existing lipid disease, to observe the variation in values, and to calculate the mean untreated value for each patient. In 'apparently' healthy untreated post-menopausal women, the values for the various lipid and lipoprotein moieties may vary considerably and yet remain within the normal range (see data for reference group in Figs. 1–5).

Although the exact variation in bioavailability for dydrogesterone is not known, a 5-fold difference in plasma levels after administration of other progestogens has been reported (Fotherby 1983). We would be surprised if there were not some overlap in the range of plasma levels achieved with the 10 mg and 20 mg doses of dydrogesterone. We used each woman as her own control in a cross-over design and were unable to demonstrate a dose-dependent effect of dydrogesterone on lipids and lipoproteins.

The final assessment took place after 2 months of treatment with conjugated equine oestrogens alone, and was included to determine whether omission of the dydrogesterone in months 8 and 9 influenced lipid and lipoprotein metabolism. Most previous investigations of the effects of combined oestrogen/progestogen regimens have not attempted to distingush between the effects of oestrogen and progestogen.

Many factors can influence lipid and lipoprotein levels; these include weight, smoking habit, caffeine and alcohol intake and a febrile illness. Non-patient factors include method of venepuncture, transportation of the sample and laboratory methods. We made every effort to minimize the impact of all these potential confounders. We are unhappy with our coefficient of variation for HDL_2-cholesterol which was high both within (9·0–12·6%) and between batches (10·12–14·1%). We used the Beckman airfuge for separation and found this technically difficult: not surprisingly, the reproducibility was poor. Because of this, we doubt the reliability of our HDL_2-cholesterol data.

The mean pretreatment plasma total cholesterol level was 6·19 mmol/l, and this did not change significantly at any time during treatment (Table 3) but therapy reduced LDL-cholesterol (Fig. 1) by about 16% and increased HDL-cholesterol (Fig. 3) by about 17%. These data are in

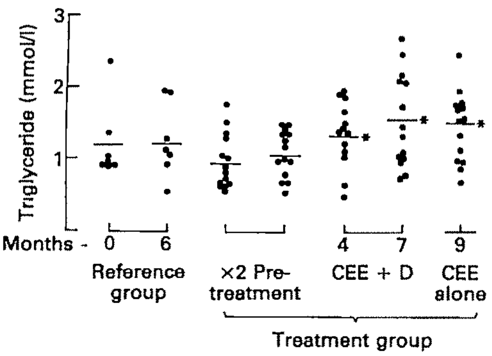

Fig. 5. Plasma triglyceride values for the treatment and reference groups. CEE = conjugated equine oestrogens. D = dydrogesterone *indicates statistically significant increase ($P<0{\cdot}001$) compared with pretreatment.

agreement with those reported by Bush & Miller (1987) who studied women taking unopposed conjugated equine oestrogens. Our results illustrate that assessment of the sub-fractions of cholesterol is much more illuminating than that of total cholesterol alone. The apolipoprotein results reflected changes in the relevant lipid fractions: thus apo A1 (the main protein fraction of HDL) was significantly increased by therapy (Fig. 4), and apo B (the predominant protein fraction of LDL) was significantly reduced (Fig. 2). Again, there were no significant differences between the combined and oestrogen-only phases of treatment. We were disappointed that 14 samples were not assayed for apo A1 and apo B because insufficient plasma remained after thawing. We set aside approximately 50–100 µl at −70°C for these analyses, but evidently this was insufficient if, as may have happened in this study, the sample tubes were not effectively sealed. We can offer no other explanation.

HDL_3-cholesterol (Table 3) and total triglyceride values (Fig. 5) were significantly elevated by treatment (although still within the normal range for our laboratory) and there were no significant differences between combined therapy and oestrogen-alone. The significance of the triglyceride changes is unclear; preliminary Finnish data indicate that HDL_3-cholesterol levels are inversely related to the risk of acute myocardial infarction (Salonen *et al.* 1988).

Significant changes were observed in the reference group for two lipid fractions; HDL_3-cholesterol was significantly lower at the second assessment and HDL_2-cholesterol was significantly higher. We can offer no explanation for the former and can only suggest that the latter change may have been due in part to imprecision of the assay and the small numbers of women assessed.

We find it difficult to compare our results with those of other groups who have reported on the lipid effects of dydrogesterone when added to postmenopausal oestrogen therapy. Soutoul *et al.* (1983) and Serfaty *et al.* (1986) reported no significant changes in either total cholesterol or HDL-cholesterol, but neither paper described the lipid methodology. De Cleyn *et al.* (1986) reported no significant change in the LDL and HDL sub-fractions—but a significant increase in apo A1. They used standard methods for measuring the latter, but electrophoresis was used for the LDL and HDL-cholesterol determinations, and we consider this inappropriate. It is difficult to reconcile a large increase in apo A1 when its binding lipid, HDL-cholesterol, is not correspondingly elevated.

Although the precise mechanisms whereby postmenopausal oestrogens reduce arterial disease risk require clarification, circumstantial evidence suggests that alterations in lipid and lipoprotein metabolism are involved (Gruchow *et al.* 1988). Thus, it is important in women with a uterus and especially for long-term use to prescribe a progestogen which has little, if any, negative impact on oestrogen-induced lipid changes. Dydrogesterone, 10 mg and 20 mg did not significantly influence apparently beneficial oestrogen-induced changes in this study.

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Endometrial, physical and psychological effects of postmenopausal oestrogen therapy with added dydrogesterone

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Summary. Sixteen postmenopausal women receiving conjugated equine oestrogens 1·25 mg/day, continuously, were randomly allocated to add dydrogesterone 20 mg/day for 12 days each calendar month for 3 months and then 10 mg/day in an identical fashion for a further 3 months, or to receive the dydrogesterone doses in reverse sequence. The effects of the two dydrogesterone doses on endometrial histology, vaginal bleeding, and the symptomatic and psychological status were compared. Endometrial samples were obtained around day 10 of progestogen addition. Dydrogesterone, 20 mg, induced uniform, late secretory transformation in all samples; with 10 mg one sample showed mixed early and late secretory features and another demonstrated late secretory changes associated with atypical hyperplasia. Both dydrogesterone doses induced an acceptable withdrawal bleed; most bleeding episodes were 'spotting' or normal in amount, and heavy bleeding was reported infrequently. There was one episode of breakthrough bleeding. There were no differences in bleeding patterns between the two dose regimens. Anxiety, and the physical and psychological status were significantly improved after 3 months of therapy. Significant benefits on depression were observed less clearly. There were no differences between the two dydrogesterone doses on anxiety, depression and the physical and psychological status, and, overall, the addition of the progestogen did not antagonize oestrogen benefits.

In women with an intact uterus, climacteric symptoms are most commonly treated by a combination of a 'natural' oestrogen with progestogen added sequentially. Such treatment is also the optimal form of therapy for the prevention of postmenopausal bone loss and its related fractures (Consensus Development Conference, 1987). For this indication, our current under-

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standing is that treatment needs to be prescribed for a minimum of 5 years so safety is extremely important.

The choice of progestogen requires a consideration of efficacy, acceptability and safety. It must be sufficiently potent to prevent endometrial abnormalities and thus obviate the increased risk of endometrial cancer associated with unopposed oestrogen therapy (Peterson *et al.* 1987; Whitehead & Fraser, 1987). Ideally, it should not produce premenstrual like side-effects which might reduce compliance (Magos *et al.* 1986). Additionally, it should not negate the beneficial lipoprotein profile produced by oestrogen treatment which is probably a predominant reason for the reduction in arterial disease risk seen in patients taking oestrogens long-term (Stampfer *et al.* 1985; Bush *et al.* 1987; Ross *et al.* 1987).

We have reported previously that dydrogesterone (Duphaston; Duphar Laboratories, Southampton) is a potent progestogen and at a dosage of 20 mg daily induced uniform secretory change in endometrial samples obtained after 6 days of administration (Lane *et al.* 1986*a*). This study, however, did not show uniform secretory change with 10 mg daily. This could be due to the lower dose being inadequate or to the timing of endometrial sampling. The lower dose might require longer duration, perhaps 10–12 days before uniform responses are achieved. The optimal duration of progestogen addition to prevent hyperplasia is now known to be at least 12 days each cycle (Studd *et al.* 1980; Whitehead *et al* 1982).

Therefore, we have investigated the endometrial effects of 20 mg and 10 mg of dydrogesterone, daily, in the same patients in a randomized, double-blind, cross-over study: the endometrial samples were collected around day 10 of progestogen addition. Data were also collected on progestogen-induced symptomatic and psychological side-effects. Effects on lipid, lipoprotein and triglyceride metabolism were also determined (Siddle *et al.* 1990).

Subjects and methods

Full details of the women and treatment regimens are described in the previous article (Siddle *et al.* 1990). We recruited 16, symptomatic, women with an intact uterus and with FSH levels within the postmenopausal range; 15 of them had not menstruated for at least 6 months and one had menstruated 4 months previously. None had received oestrogen or progestogen therapy during the previous 6 months or had experienced abnormal vaginal bleeding. All had a pretreatment endometrial biopsy showing no abnormal features.

Each woman received conjugated equine oestrogens (CEE) (Premarin Wyeth/Ayerst, Maidenhead) 1·25 mg daily continuously for 9 months. After the first month, eight were randomly allocated to receive 20 mg of dydrogesterone daily for the first 12 days of each month for the next 3 months, and then 10 mg of dydrogesterone daily in an identical fashion for a further 3 months (group 1). The other eight women received the two dosages of dydrogesterone in reverse order (group 2). CEE alone were administered for the last 2 months. Medication was packaged to include placebo tablets so that the dydrogesterone dosage was unknown to both patient and investigator.

Three endometrial biopsies were taken, the first before treatment to exclude endometrial abnormality, and the other two around day 10 of dydrogesterone addition in months 4 and 7, at the end of the 3 months of treatment with the two different doses. All tissue was immediately placed into buffered neutral formalin. Specimens were stained with haematoxylin and eosin and examined by light microscopy as described previously (Lane *et al.* 1986*a*). The features assessed were those of the normal menstrual cycle.

Each woman completed a diary card every day. All bleeding was recorded and was scored subjectively as 1 = spotting, 2 = normal bleeding and 3 = heavy bleeding. Withdrawal bleeding was defined as that occurring towards the end of or immediately after the phase of progestogen addition: all other bleeding episodes were classified as breakthrough. The diary card was also used to record tablet ingestion and served to check compliance.

Symptomatic and psychological variables were assessed with a modified, 31 item symptom questionnaire derived from the Leeds Scale (Snaith *et al.* 1976). In addition to the 12 standard questions relating to anxious and depressed mood, 19 questions were included about psychological attitudes and physical symptoms thought likely to be influenced by oestrogen/progestogen therapy (Table 1).

The questionnaire was completed on seven occasions: before treatment, at the end of month

Table 1. Symptom questionnaire

I feel tired
I have headaches
I am suffering from acne
I have hot flushes
I feel relaxed
I have dizzy spells
My breasts feel tender or uncomfortable
I feel happy
I suffer from vaginal dryness
My stomach feels bloated
I suffer from backache
I have abdominal cramps or discomfort
I am more clumsy than usual
My skin or hair is more greasy than usual
I feel sick or nauseous
My memory is good
I still desire sexual intercourse
I have difficulty in getting off to sleep
I have pains in my joints or limbs

1 after 28 days of CEE therapy alone, and twice in months 3 and 6,—between days 8 and 10 of CEE/dydrogesterone administration and again at the end of CEE-alone treatment. The final assessment was performed at the end of month 9 after 2 months of CEE-alone. The questions were answered on a four point scale: 'definitely', 'sometimes', 'not much', or 'not at all'. These responses were subsequently scored on a four point scale in such a way that the highest potential score was always awarded to the most negative response.

Statistical analyses

Statistical analyses of the symptom questionnaires were performed using an analysis of variance on the results of the 7 assessments. Differences between assessments were investigated by a comparison of the mean values between the assessments, not taking into account different dose levels.

The differences between the dydrogesterone doses were examined using Tukey's least significant difference multiple comparison test to compare pre-treatment with on-treatment means.

Results

The characteristics of the women in the study are given in the previous paper (Siddle *et al.* 1990). Two women were lost to the study, one defaulter and one protocol violator.

Endometrial histology

Before treatment, no curettings were obtained from seven (43%) of the 16 women. One sample showed late secretory changes. Non-secretory endometrium was diagnosed in one woman and is defined as proliferative endometrium without mitosis (Table 2).

The third biopsy in group 1 (on dydrogesterone 10 mg daily) showed four uniform late secretory samples, one sample with late and co-existing early secretory features, one sample with late secretory changes with a small area of atypical hyperplasia, and no curettings were obtained from one patient. Atypical hyperplasia was diagnosed because of the presence of hyperplastic, crowded eosinophilic glands with nuclear stratification and mild nuclear atypia.

Endometrial biopsies were not attempted on two occasions in group 2 because withdrawal bleeding had already started.

Patterns of bleeding

Acceptable withdrawal bleeding was experi-

Table 2. Endometrial histology in postmenopausal women treated with oestrogen/dydrogesterone

		Month of treatment			
		4		7	
Endometrial diagnosis	Pretreatment	Group 1	Group 2*	Group 1	Group 2*
No curettings	7	–	–	1	–
Proliferative	5	–	–	–	–
Non-secretory	1	–	–	–	–
Late secretory	1	7	6	6†	6

* One biopsy not attempted because patient already bleeding.

† Includes one sample showing co-existing atypical hyperplasia and another with co-existing early secretory changes.

Treatment protocol: All the women received 1·25 mg of conjugated equine oestrogens daily for 9 months with additional dydrogesterone on days 1–12 of months 2–7; group 1 received 20 mg during months 2–4 and then 10 mg during months 5–7, group 2 received the two dosages of dydrogesterone in reverse order.

Table 3. Duration of bleeding episodes in menopausal women receiving oestrogen therapy with added dydrogesterone

	Mean no. of days of							
	Spotting		Normal bleeding		Heavy bleeding		Total bleeding	
Month of treatment	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
2	2·9	3·1	2·6	4·0	1·6	2·0	7·0	9·1
3	2·0	1·7	2·0	2·1	0·6	1·4	4·6	5·3
4	2·6	3·1	2·5	2·4	1·1	0·1	6·2	5·7
5	1·7	2·4	2·9	2·6	0·9	1·0	5·4	6·0
6	1·0	2·7	3·1	2·1	0·6	1·1	4·7	6·0
7	1·3	2·4	2·9	2·4	0·3	0·9	4·4	5·7

Treatment protocol: In addition to 1·25 mg of conjugated equine oestrogen daily the women in group 1 received 20 mg of dydrogesterone on days 1–12 during treatment months 2–4 and then 10 mg of dydrogesterone during months 5–7. The women in group 2 received the same treatment but the two doses of dydrogesterone in reverse order.

enced in every month except on three occasions. One woman in group 2 had a withdrawal bleed which started immediately after the phase of progestogen administration but continued for 25 days. The latter part of this episode must be considered unscheduled bleeding, it occurred after treatment month 4 when she changed from 10 mg of dydrogesterone to 20 mg daily. The other two exceptions were amenorrhoea reported by two women, both in month 7 when one was taking 10 mg of dydrogesterone and the other 20 mg daily.

The mean duration of 'spotting', normal and heavy bleeding by treatment month is shown in Table 3. Most episodes were 'spotting' or normal in amount, and heavy bleeding was reported infrequently. Bleeding was longest in the first month of dydrogesterone addition, irrespective of the dose. There were no statistically significant differences in the duration of bleeding between the doses of dydrogesterone, and there were no obvious trends over time. The mean duration of total bleeding for all women when taking dydrogesterone 10 mg was 6·3 days, and 5·4 days with 20 mg daily.

Symptomatic and psychological assessments

All the questionnaires were completed at the appropriate times. The results are shown in Table 4. The physical and psychological scores represent the answers to the questions shown in Table 1. The anxiety and depression scores are from the Leeds Scale. For comparisons, these data are presented according to dydrogesterone treatment schedule.

With all three scores, the relatively large standard deviations indicate a wide variation between women. The major effect of therapy was to reduce all scores with a trend for a continuing reduction with increasing duration of use. For anxiety, differences between the means of >2·2 were significant at the 5% level: thus, compared with pretreatment there was a significant beneficial effect at the CEE-alone assessment in month 3 and this continued until the end of the study. The variation in the depression scores was greater than that for anxiety scores and a difference between means of approximately 2·5 was required to achieve a least significant difference at the 5% level: the mean values, on CEE-alone at months 3 and 9 were significantly lower than pretreatment values. The physical and psychological scores showed a highly significant downwards trend. The least significant difference at the 5% level between any pair of means was 5·7; compared with pretreatment values there was a significant reduction at the CEE/dydrogesterone assessment in month 3 and in all subsequent assessments.

No significant differences were observed between the two dydrogesterone doses, nor between the CEE and CEE/dydrogesterone phases of treatment for anxiety, depression and the physical psychological assessments.

The 19 physical and psychological assessments (Table 1) were examined individually to determine whether differences existed between the CEE-alone and CEE/dydrogesterone phases. Too few 'adverse' effects due to dydrogesterone addition were observed for meaningful analysis, for example, whether the progestogen increased breast tenderness.

Table 4. Symptomatic and psychological assessment during post menopausal oestrogen therapy with added dydrogesterone

Variable	Pre-treatment	Months of treatment						5% least difference between means
		1	3		6		9	
		CEE	CEE+DYD	CEE	CEE+DYD	CEE	CEE	
Anxiety score								
Group 1	6·86	5·29	5·29	4·88	3·57	3·86	3·29	
	(4·18)	(1·98)	(2·14)	(2·85)	(3·46)	(3·08)	(1·80)	
Group 2	6·29	4·57	4·86	3·71	4·57	3·33	4·00	
	(2·29)	(3·64)	(5·87)	(3·04)	(2·57)	(3·39)	(2·89)	
Groups 1+2	6·57	4·93	5·57	4·21*	3·93*	3·21†	3·64†	2·2
	(3·25)	(2·84)	(4·01)	(2·96)	(3·00)	(3·15)	(2·34)	
Depression score								
Group 1	7·57	6·29	6·86	4·57	5·29	5·00	4·29	
	(5·00)	(3·77)	(3·34)	(4·16)	(5·09)	(5·77)	(2·81)	
Group 2	6·14	6·14	6·00	4·29	6·43	5·83	4·57	
	(4·10)	(4·60)	(4·51)	(4·35)	(4·65)	(4·79)	(2·15)	
Groups 1+2	6·86	6·21	6·43	4·43*	5·86	5·38	4·43*	2·5
	(4·45)	(4·04)	(3·84)	(4·09)	(4·72)	(5·14)	(2·41)	
Physical and psychological score								
Group 1	25·57	19	20·3	17·0	14·4	15·0	14·86	
	(7·81)	(6·51)	(2·75)	(9·11)	(9·03)	(7·89)	(7·65)	
Group 2	27·4	24·6	20·3	20·57	19·7	20·3	20·0	
	(6·99)	(4·69)	(10·9)	(9·03)	(8·75)	(8·48)	(1·63)	
Groups 1+2	26·5	21·8	20·3†	18·78†	17·07†	17·46†	17·43†	5·7
	(7·19)	(6·17)	(7·65)	(8·91)	(8·97)	(8·20)	(5·94)	

Treatment protocol: All the women received 1·25 mg of conjugated equine oestrogens (CEE) daily for 9 months with additional dydrogesterone (DYD) on days 1–12 of months 2–7, group 1 received 20 mg during months 2–4 and then 10 mg during months 5–7, group 2 received the two dosages of dydrogesterone in reverse order

Results are mean (SD) values Statistically significant from pretreatment values (ANOVA with Tukey's procedure) *at the 5% level, †at the 1% level

Discussion

All endometrial samples obtained during 20 mg of dydrogesterone therapy showed uniform secretory changes and these would be expected after 10 days exposure to a potent progestogen. Ten of the 12 samples obtained during 10 mg of dydrogesterone therapy showed identical uniform changes but two showed co-existing but different histological appearances, one being focal atypical hyperplasia and the other early secretory features. The latter result can only be explained by a sub-optimal progestational stimulus. The co-existing hyperplasia could also be due to this, but it could also have arisen before treatment and not been detected at the two previous biopsies when no curettings (pretreatment biopsy) and uniform late secretory endometrium (second biopsy) were diagnosed. We consider the second explanation less likely. We have reported previously that women differ in their responses to norethisterone and norgestrel (Whitehead *et al.* 1987; Fraser *et al.* 1989), oral progesterone (Lane *et al.* 1983) and medroxyprogesterone acetate (Lane *et al.* 1986*b*), with some endometrial samples exhibiting full secretory responses and others incomplete changes to a given dose. Therefore, we see no reason why dydrogesterone should not cause a range of endometrial responses. We conclude that whereas 10 mg of dydrogesterone daily is an adequate dose for most women who receive 1·25 mg/day of CEE some will need 20 mg daily for full secretory change. An alternative conclusion would be that because the protective mechanism of action of progestogens is unknown and could be due to suppression of mitotic activity as well as endometrial sloughing, then all that is required is suppression of cellular mitosis and full secretory transformation is unnecessary. This is an attractive hypothesis, and it will remain so unless convincing data are presented showing that minimal/incomplete secretory transformation is associated with an increased incidence of cancer in the long-term. Biochemically, atypical hyperplasia unlike the cystic form exhibits abnormal activity (King *et al.* 1979), and it carries a risk of subsequent malignant change. We believe that every effort should be made to suppress its development.

Both dydrogesterone doses induced an acceptable bleeding pattern. Most bleeding episodes were normal or 'spotting', and heavy bleeding occurred infrequently. Interestingly, heavy bleeding was reported more commonly and the total duration of bleeding was longest after the first exposure to dydrogesterone irrespective of dose (Table 3). We suspect that this represents chronic, low-grade endometrial stimulation due to endogenous oestradiol: the two patients with the heaviest bleeding at this time (both 11 days) had proliferative endometrium at the pretreatment biopsy. We believe that women should be warned that their first bleed may be heavy.

Significant improvements in anxiety and the physical and psychological scores were achieved by the third treatment month but not immediately. Although similar trends were observed with depression, because of the greater variation in response between women, statistically significant improvements at the 5% level were observed only at 9 months, but at the 1% level for anxiety. There were no significant differences between the dydrogesterone doses, nor between the CEE and CEE/dydrogesterone treatment phases for all three sets of assessments.

The study design would have identified any symptom that occurred frequently during dydrogesterone addition and had a dose response relation. With an 80% power of detection, the sample size used in this study could detect reductions of about 20% (relative to pretreatment) in the physical and psychological scores. Similarly, the sample size could detect a reduction of 30% in anxiety and depression scores. These calculations were based upon the relation between the power and the true difference/standard error (Hills & Armitage, 1979). A clinically significant change would be in the order of 25–30%, and changes of this magnitude were observed at various times in the anxiety, depression, and physical and psychological scores (Table 4).

In clinical practice, women complain of symptoms during the progestogen phase of combined treatment. A previous, unpublished cross-sectional study (Siddle & Whitehead) suggested that side-effects may be limited to a sub-section of women, with perhaps 5–10% experiencing a premenstrual type syndrome induced by progestogens. A similar observation was made when 5 mg of norethisterone daily was added sequentially to postmenopausal oestrogen therapy (Magos *et al.* 1986). Thus, we included questions relating to abdominal bloating, breast tenderness, greasy skin etc, in our symptom questionnaire. However, in this study no woman reported a collection of physical symptoms or showed evidence of a dose-response relation, but this study cannot exclude the possibility that a small number of women might experience occasional adverse symptoms when dydrogesterone is added.

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A longitudinal study of platelet behaviour and thromboxane production in whole blood in normal pregnancy and the puerperium

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Summary. A longitudinal study of platelet behaviour (platelet aggregation and release reaction) in whole blood and of serum thromboxane B_2 production was performed before, during and after normal pregnancy. The response of platelets to arachidonic acid and to adrenaline was significantly increased in the third trimester. Six weeks after delivery, values were still modestly increased but return to non-pregnant values was complete by 12 weeks. Serum thromboxane B_2 production was unchanged throughout pregnancy and the puerperium.

Previous studies have shown increased platelet reactivity in normal pregnancy (Yamazaki *et al* 1979, Lewis *et al.* 1980, Hoche *et al* 1983, Andrews *et al.* 1985, Morrison *et al.* 1985, Leuschen *et al.* 1986). Such reports have involved study of platelet behaviour in platelet-rich plasma, and the increased platelet activity has been demonstrated either in comparison with non-pregnant controls or in comparison with values obtained for the same women post-partum.

The importance of a proper understanding of platelet reactivity in normal pregnancy rests not only with the possible contribution of platelets to the hyper-coagulable state and increased thrombo-embolic risk at this time, but perhaps more importantly in the interpretation of changes seen in pre-eclampsia. Platelets have been implicated in the aetiology of this condition (Howie *et al.* 1971) and may be involved in the formation of micro-thrombi in the utero-placental circulation. This would be exacerbated by the release from platelets of thromboxane A_2 (TxA_2) which is itself both a potent promoter of platelet aggregation and a vasoconstrictor. It has been suggested that enhanced TxA_2 synthesis may have a role in the pathogenesis of pre-eclampsia (Fitzgerald *et al.* 1990). Moreover, anti-platelet agents have been successful in preventing pre-eclampsia in selected cases (Beaufils *et al.* 1985, Wallenburg *et al.* 1986, Schiff *et al.* 1989).

We have undertaken a longitudinal study of platelet aggregation and the platelet release reaction in whole blood that occurs in response to several different aggregating agents, during normal pregnancy. We have also measured serum thromboxane B_2 (TxB_2) production, the major stable metabolite of TxA_2. These data describe the physiology of platelet behaviour during normal pregnancy employing methods to study platelets that are more physiological than

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those described previously using platelet-rich plasma. If platelets are involved in the pathogenesis of pre-eclampsia, an appreciation of the nature, time of onset and time of resolution of any changes that occur in normal pregnancy will form the background against which subsequent observations in hypertensive pregnancy, and in the use of low dose aspirin, may be interpreted.

Subjects and methods

Forty nulliparous women who were hoping to conceive were recruited from either general practice or the hospital sub-fertility clinic. The eight women from whom complete data were subsequently obtained were studied before, during and after normal pregnancy. No subject gave a history of essential hypertension, renal disease or usage of drugs known to influence platelet behaviour. None of the pregnancies was complicated by hypertension, preterm delivery or poor fetal growth.

As the methods to investigate the platelet release reaction were not established when the women were originally recruited, an alternative control group was required for this test. Rather than rely on 12 week postnatal values for use as an internal control with the assumption that all the changes of pregnancy would have returned to normal by this time, a control group of 12 normal non-pregnant women volunteers was recruited.

Study design

Women were studied before conception, and again at 12, 16, 28, 32 and 36 weeks gestation. Further studies were performed at both 6 and 12 weeks postnatally. On each occasion, platelet aggregation and TxB_2 were measured. Platelet release reaction was measured on every occasion during pregnancy and postnatally, and also in the 12 non-pregnant volunteers.

Materials

Solutions of aggregating agents were kept at 0°C, and when they were added to whole blood their final concentrations were as follows: arachidonic acid 0·2 mM, adrenaline 1 μM, adenosine diphosphate (ADP) 0·5 μM, platelet activating factor 0·03 μM, collagen 1 μg/ml and U46619 (a synthetic thromboxane A_2 mimetic) 0·3 μM. Saline (150 mM) was used as a control.

Blood collection

Blood was collected by clean venepuncture, using a 19 gauge needle. Duplicate 9 ml aliquots were immediately anticoagulated with 1:10 3·13% w/v trisodium citrate dihydrate; one aliquot contained 6 μl of ^{14}C-labelled serotonin in addition. These were incubated at 37°C along with clotted and EDTA blood samples.

Platelet aggregation

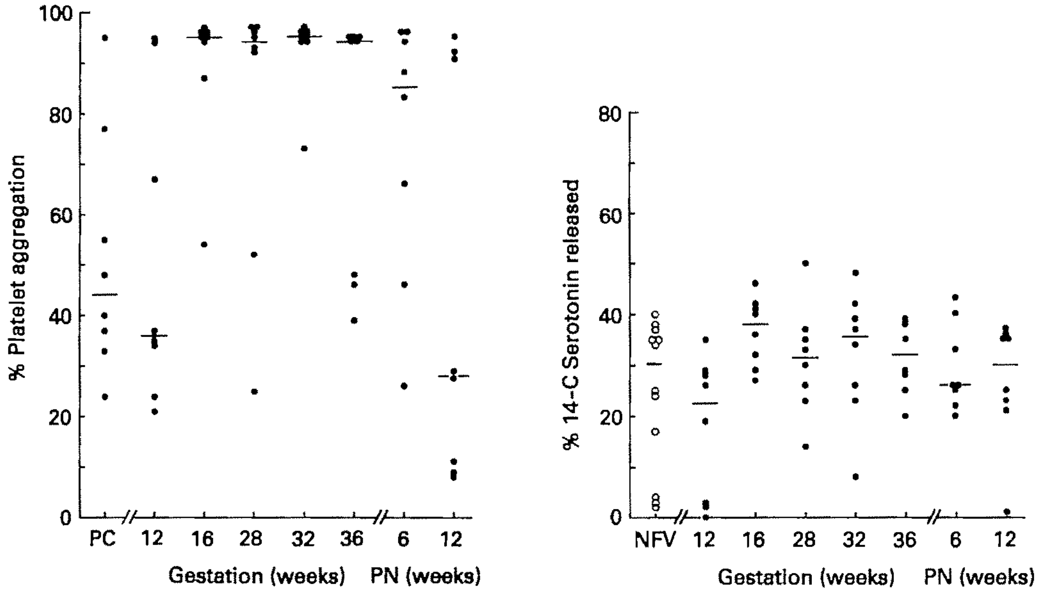
The extent of platelet aggregation, after the addition of each aggregating agent to samples of stirred whole blood, was measured using a platelet counting technique. After a 20-min period, a series of 480 μl samples of whole blood was stirred (1000 rpm) for 2 min before 20 μl of an aggregating agent was added to each. Repeated 15 μl aliquots were withdrawn subsequently from each blood sample at 10 s intervals for 1 min, then at 2, 4, and 8 min, and mixed with 30 μl of fixative solution. The number of single free platelets was then counted by the Ultra-Flo 100 Whole Blood Platelet Counter. Platelet aggregation was expressed as the proportion of single free platelets remaining, compared with the total number of platelets in the original EDTA sample (in which platelets do not aggregate). Hence a series of platelet aggregation versus time curves was obtained for each aggregating agent over the course of the pregnancy.

Release reaction

The amount of ^{14}C-labelled serotonin released from the pre-labelled platelets after the addition of each of the aggregating agents was also determined. The above method was repeated, but aggregation was terminated after 6 min by cessation of stirring, addition of an aspirin solution, and cooling to 0°C. The samples were then centrifuged before duplicate 50 μl aliquots of the supernatant were removed for scintillation counting. The release reaction was expressed as the percentage of the total radioactivity released from the pre-labelled platelets after addition of each aggregating agent. Allowance was made for the haematocrit of individual samples.

Serum TxB_2 production

Serum was removed from the blood that had been allowed to clot at 37°C for 60 min and was then frozen at −50°C. These samples were later



(a) (b)

Fig. 1. Platelet aggregation (a) after 2 min and release reaction (b) in response to 0·2 mmol/l arachidonic acid pre-conception (PC), during pregnancy and post-natally (PN) and in non-pregnant female volunteers (NFV). Median values are shown. The increased aggregation during pregnancy was statistically significant ($P < 0{\cdot}01$) at 32 weeks gestation.

thawed and assayed using radioimmunoassay kits from Amersham International. Results were expressed as nmol TxB_2 per 10^9 platelets. The intra-assay coefficient of variation was 16·2% (over 30 samples), and the inter-assay coefficients of variation were 16·2% for a mean value of 0·82 ng $TxB_2/10^9$ platelets, 12·3% for a mean value of 0·65 ng $TxB_2/10^9$ platelets, and 9·8% for a mean value of 0·04 ng $TxB_2/10^9$ platelets, over eight assays, and using samples chosen to cover the range of values encountered in this study.

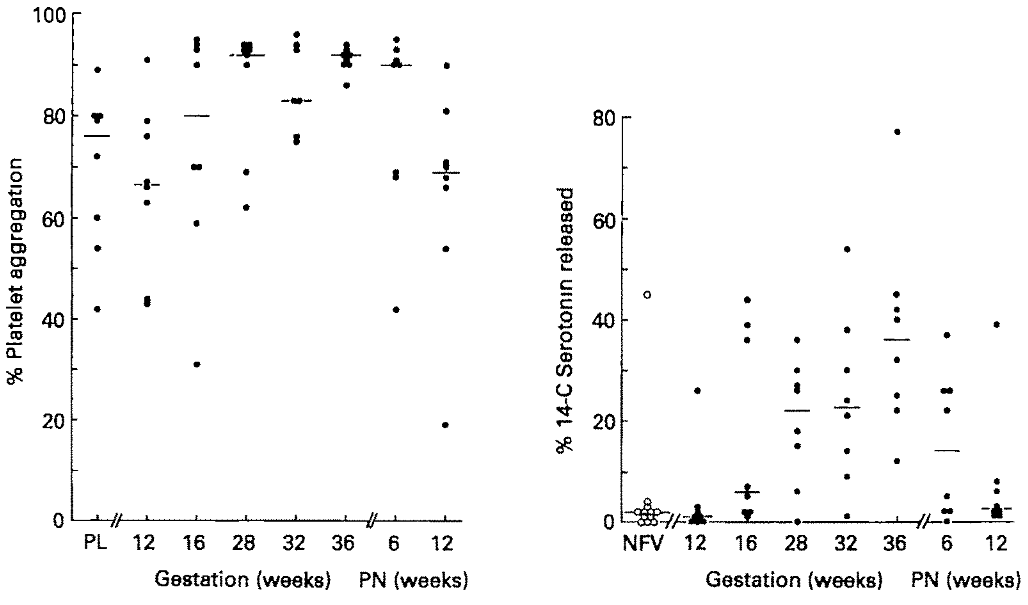
Statistics

As the sample size is small, and the data tended not to be normally distributed, medians have been used as the estimate of central tendency. Wilcoxon matched pairs signed-rank tests have been employed, avoiding assumptions concerning the distribution of the data. Statistical significance has been taken as $P < 0{\cdot}01$, to allow for the repeated use of individual statistical tests. Unpaired analysis with the Mann-Whitney *U*-test was used when comparing release reaction results from the main study group with the non-pregnant female volunteers.

Results

Platelet aggregation

No significant changes were noted in platelet aggregation induced by saline, ADP, platelet activating factor, collagen or U46619, when pregnancy and post-natal values were compared with those obtained before conception. A trend towards increased arachidonic acid-induced platelet aggregation was statistically significant at 32 weeks gestation ($P<0{\cdot}01$). The return of the increased values at 32 weeks to non-pregnant levels appeared incomplete at 6 weeks post-partum. These findings are illustrated in Fig. 1a. Adrenaline-induced platelet aggregation followed a similar pattern to that seen with arachidonic acid, with statistically significant increases observed at all times after the addition of the aggregating agent to blood taken at 28 weeks gestation, and also at 4 min after stimulating the platelets in blood taken at 32 and 36 weeks gestation (each $P<0{\cdot}01$). As seen for arachidonic acid, the return to non-pregnant values appeared to be incomplete at 6 weeks post



(a) (b)

Fig. 2. Platelet aggregation (a) after 4 min and release reaction (b) in response to 1 μmol/l adrenaline preconception (PC), during pregnancy and post-natally (PN) and in non-pregnant female volunteers (NFV) Median values are shown. The increased aggregation and release during pregnancy were statistically significant ($P < 0{\cdot}01$) at 28, 32 and 36 weeks gestation.

delivery. These results are illustrated in Figure 2a.

Release reaction

The extent of the release reaction induced by arachidonic acid did not increase significantly during pregnancy (Fig. 1b) but there was a significant increase in the extent of the release reaction induced by adrenaline, at 28, 32 and 36 weeks (each $P < 0{\cdot}01$), as for platelet aggregation. Return to non-pregnant values was again incomplete 6 weeks after delivery (Fig. 2b). No significant changes in the release reaction were observed when saline, ADP, platelet activating factor, collagen or U46619 were used as the aggregating agents.

Serum TxB_2 production

No significant changes in serum TxB_2 production were seen during pregnancy or the puerperium (Fig 3).

Discussion

We have measured changes in platelet aggregation, the release reaction and serum TxB_2 production serially, throughout normal pregnancy and the puerperium. The whole blood technique which we employed is more physiological than

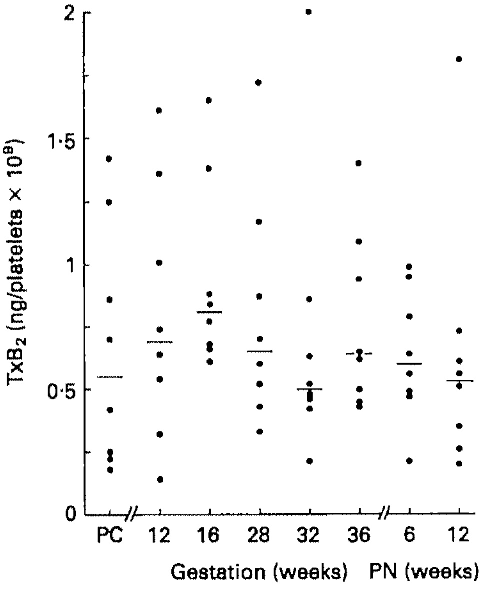


Fig. 3. Serum thromboxane B_2 production preconception (PC), during pregnancy and post-natally (PN) Median values are shown.

methods using the more conventional platelet-rich plasma, as centrifugation, with the removal of both the largest and most active platelets and the interactive red and white cells (Gaarder *et al.* 1961, Blackwell *et al.* 1978), is not required, and platelets remain in their natural environment. Our experiments showed incomplete resolution of pregnancy-induced changes in platelet aggregation at 6 weeks after delivery and this suggests that the use of such puerperal values as controls (as used in some previous investigations) is of questionable value. If post-natal values must be used as controls, 12 weeks should elapse from the time of delivery.

Whigham *et al.* (1978), using platelet-rich plasma, found that platelet aggregation induced by a wide variety of aggregating agents was unchanged in normal pregnancy, but most other workers have suggested that platelets are more active. Increased adrenaline-induced platelet aggregation has been described at various gestations (Yamazaki *et al.* 1979; Leuschen *et al.* 1986). Our results agree with previous findings using adrenaline as the aggregating agent and show increased platelet aggregation and release reaction at 28, 32 and 36 weeks. In contrast to Lewis *et al.* (1983), we did not find increased platelet aggregation with ADP. However, that group used considerably higher concentrations of ADP, up to 10 µM, compared with 0·5 µM in our experiments. We are in agreement with others (Hoche *et al.* 1983, Greer *et al.* 1988) who have been unable to demonstrate any change in ADP-induced platelet aggregation in platelet-rich plasma and whole blood, respectively. Our finding that platelets are more reactive to arachidonic acid stimulation in normal pregnancy confirms the work of Andrews *et al.* (1985), Morrison *et al.* (1985) and Leuschen *et al.* (1986).

Arachidonic acid binds reversibly to plasma albumin (Lucas *et al.* 1986), and a reduced concentration of this protein could explain our findings of increased aggregation with arachidonic acid during pregnancy, if, as a consequence, increased concentrations of free arachidonic acid were available for stimulation of platelet aggregation. However, we were unable to identify any such inverse correlation in three women chosen for their typical aggregation findings during the pregnancy. This confirms our previous findings (Morrison *et al.* 1985).

Results of measurements of collagen-induced platelet aggregation during pregnancy have been inconsistent (Leuschen *et al.* 1986). Our own failure to demonstrate any pregnancy-induced changes with collagen may have resulted from the relatively high dose which was chosen (1 µg/ml), which, in retrospect, probably achieved near maximal responses even before conception. This is despite the partially shared mechanism of action of arachidonic acid and collagen in platelet activation via the generation of TxA_2 (Carter *et al.* 1985). Similarly, near maximal responses to U46619 were achieved in many of the women studied, before conception. We found no change in median U46619-induced platelet aggregation in pregnancy. However, in those women who had demonstrated relatively weak responses before conception, we did see an increase in U46619-induced platelet aggregation, which was most marked at 28 weeks. Although there was no significant change in the median value, it is tempting to speculate that an increased sensitivity of the platelets to TxA_2 was responsible for this trend, which might explain the increased aggregation seen with arachidonic acid and adrenaline.

Adrenaline-induced release reaction was markedly increased during the third trimester of pregnancy and, as with platelet aggregation, this effect did not completely resolve until 12 weeks post-partum. As far as we are aware, the release reaction in whole blood during pregnancy has not been investigated before, and consequently, this is a new finding. Using a similar labelling technique, but with platelet-rich plasma, Morrison *et al.* (1985) found no change in arachidonic-induced release reaction in late pregnancy compared with 6 weeks after delivery. This agrees with our findings using whole blood. Our finding that arachidonic acid-induced aggregation is increased during pregnancy whereas the release reaction is not increased, is probably a reflection of the all-or-nothing nature of the release reaction response (Andrews *et al.* 1985).

One may speculate about the mechanism of the increased platelet reactivity that we found in normal pregnancy. It is interesting that those aspects of platelet behaviour that were most clearly changed during pregnancy and the puerperium (aggregation in response to adrenaline and arachidonic acid and release in response to adrenaline) depend to some extent on TxA_2 synthesis. Indeed, the release reaction induced by adrenaline is totally dependent on TxA_2 synthesis and is completely inhibited by an inhibitor of TxA_2 synthesis such as aspirin. This suggests that one or more of the steps in the synthetic pathway may be enhanced in normal pregnancy. Arachidonic acid is cleaved from phospholipids by phospholipase A_2 and acts as the substrate for the platelet enzyme cyclo-oxygenase (inhibited by aspirin) that generates the cyclic prostaglandin endoperoxides PGG_2 and PGH_2. Thromboxane synthetase is responsible for the subsequent formation of TxA_2, which in turn contributes to platelet aggregation. The individual steps in the generation of TxA_2 may be enhanced by increases in availability of substrate or enzyme activity, whilst increased sensitivity to TxA_2, or reduced metabolic clearance could also be involved. Our data are not conclusive in this regard, but the results obtained using U46619 suggest that an increased receptor sensitivity to TxA_2 could contribute to the increased platelet responses that we have observed. Kilby *et al.* (1989) noted an increase in basal concentration of intracellular free calcium ions during pregnancy and this may be relevant to our finding of increased platelet reactivity.

Our observation of unchanged serum TxB_2 production throughout pregnancy and the puerperium agrees with findings by Koullapis *et al.* (1982), but not with Mitchell *et al.* (1978) and Greer *et al.* (1985). However, these authors measured TxB_2 in plasma rather than in serum. A study of urinary metabolites using gas chromatography-mass spectrometry showed an increase in platelet thromboxane production from 20 weeks gestation (Fitzgerald *et al.* 1987). Our technique reflects total platelet TxB_2 production and does not attempt to measure 'circulating' levels of the locally acting TxA_2. The difficulty of obtaining valid measurements of the activity of an unstable tissue hormone continues to hinder the interpretation of these data.

In conclusion, we have studied platelet behaviour in whole blood, a technique which is physiologically more valid than the use of platelet-rich plasma and have used a longitudinal study design, hence avoiding the use of post-natal control values. We have demonstrated increases in platelet reactivity in the third trimester of normal pregnancy; these changes appear to begin at 16 weeks, and complete resolution does not occur until 12 weeks postpartum. These results were obtained when platelets are stimulated by certain agents, notably arachidonic acid and adrenaline; TxA_2 synthesis contributes to the platelet response seen with both of these agents. TxA_2 has been implicated in the pathophysiology of pre-eclampsia (Wallenburg *et al.* 1986) and further studies of the factors responsible for the control of platelet reactivity may help us to understand this enigmatic condition.

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Polyhydramnios and associated maternal and fetal complications in singleton pregnancies

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Summary. During the 10-year period 1 January 1979 to 31 December 1988, polyhydramnios occurred in 537 patients with singleton pregnancies delivered at the Mercy Maternity Hospital. Associated maternal and fetal complications and the perinatal outcome of these pregnancies with polyhydramnios were analysed. In 248 of the 537 pregnancies (46%) in this group there were no maternal complications or fetal malformations and the perinatal mortality (PNM) rate was 2·4%. The PNM rate increased significantly to 13·1% when there was associated pre-eclampsia, 10% with gestational diabetes, and to 7·6% with miscellaneous complications. When polyhydramnios was associated with a fetal or placental malformation the PNM rate was 61·4%. The commonest malformations were central nervous system (31%), musculoskeletal (12%) and gastrointestinal system anomalies (10%). Placental chorioangioma occurred in two patients (0·4%) and both babies died. In women with low oestriol excretion (18% of the 455 tested) the PNM rate increased five times to 22·7%.

Polyhydramnios occurs in 0·4%–1·2% of pregnancies (Macafee 1950; Queenan & Gadow 1970) and it is associated with a high perinatal mortality rate due to fetal malformations and immaturity, it is also associated with diabetes and possibly with pre-eclampsia.

This study analyses these and other associations of the various types of polyhydramnios in 51 022 consecutive singleton pregnancies managed at the Mercy Maternity Hospital, Melbourne, during the 10-years, 1979–1988.

Subjects and methods

From 1 January 1979 to 31 December 1988, there were 51 022 singleton deliveries at the Mercy Maternity Hospital. Coding for polyhydramnios and other obstetric complications was carried out after delivery. All histories where polyhydramnios was recorded were reviewed to verify the diagnosis and the 537 resulting cases were classified according to the rapidity of onset: acute polyhydramnios was diagnosed when there was a rapid increase of amniotic fluid resulting in an enlarged tender uterus causing pain and respiratory symptoms within 3–5 days (Queenan & Gadow 1970; Weir *et al.* 1979); subacute polyhydramnios was diagnosed when signs of excessive amniotic fluid developed over an interval of 1 to 2 weeks and associated symptoms were less severe or were difficult to differentiate from other obstetric conditions such as preterm labour or placental abruption; chronic polyhydramnios was diagnosed when there was a gradual onset of excessive amniotic fluid and, although the volume of amniotic fluid varied enormously, the associated symptoms were usually mild. In some patients

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there was clinical and/or ultrasonographic evidence of polyhydramnios during pregnancy but the excessive amniotic fluid volume returned to normal before the onset of labour.

A major congenital malformation was defined as a malformation that interfered with life or function of all or part of the infant and these were classified according to the WHO system: non-immunological hydrops fetalis was also included with congenital malformations.

Glucose tolerance testing (GTT) was performed at 30–32 weeks gestation using a 50 g glucose load. Gestational diabetes was defined as carbohydrate intolerance first recognized during pregnancy whether or not insulin was required and whether or not it persisted after delivery (International Workshop on Gestational Diabetes 1985). The criterion for diagnosis was the combination of capillary plasma glucose levels of ≥ 9 mmol/l at 1 h and ≥ 7 mmol/l at 2 h. The criterion for diagnosis of hypoglycaemia was the combination of plasma glucose levels of ≤ 4 mmol/l fasting and ≤ 3 mmol/l at 3 h Previous studies from this institution have shown that maternal hypoglycaemia has a significant positive association with perinatal mortality, fetal growth retardation and major malformations of the fetal genitourinary system. (Abell & Beischer 1976; Oats & Beischer 1986).

Urinary oestriol excretion was measured by the rapid method of Brown *et al.* (1968). The lower limit of normal was defined as a line joining 27·8 μmol/24 h (8 mg/24 h) at 30 weeks gestation and 41·6 μmol/24 h (12 mg/24 h) at 40 weeks and thereafter. This line corresponds approximately to the tenth centile for a normal obstetric population. We attempted to perform 24 h urinary oestriol estimations in all patients at 30 and 36 weeks and additionally when indicated by clinical complications. In this series only the non-booked patients and those delivered before 30 weeks gestation did not receive these routine antenatal investigations.

Pre-eclampsia was defined when two or more of the following signs were present: hypertension ≥ 140/90 mmHg, generalized oedema, proteinuria not due to contamination or urinary infection.

Antepartum haemorrhage included accidental haemorrhage which was confirmed when retroplacental clot was present on examination of the placenta after delivery. Placenta praevia was diagnosed when the placenta was felt with the examining finger in the vagina, the placenta was seen to occupy all or part of the lower uterine segment at caesarean section, or the membranes were observed to have ruptured at the edge of the placenta when the secundines were examined after vaginal delivery. A diagnosis of antepartum haemorrhage of unknown cause was made only after delivery when accidental haemorrhage and placenta praevia had been excluded.

The criterion used for the diagnosis of anaemia was a haemoglobin value of < 10 g/dl before delivery in women without antepartum haemorrhage.

In this study all infants with a birthweight of ≥ 400 g were included; a stillborn infant was defined as an infant who showed no signs of life and had a birthweight of ≥ 400 g; a neonatal death was defined as death within 28 days of birth of liveborn infant with birthweight of ≥ 400 g. The perinatal mortality rate was the number of neonatal deaths plus stillbirths per 1000 total births. (Consultative Council on Obstetric and Paediatric Mortality and Morbidity 1987).

Results

There were 537 women with polyhydramnios in singleton pregnancies. The mean gestation at onset was 31·4 weeks and at delivery 37·2 weeks; 154 patients (28·6%) were delivered preterm (<37 weeks) and 55 (77%) of all perinatal deaths occurred in this group.

In the 19 women with acute polyhydramnios the perinatal mortality rate (PNM rate) was 73·6%; the mortality rate decreased to 35.3%; when the onset was subacute (17 women) and to 11·2% when the onset was chronic (501 women). When polyhydramnios had disappeared towards the end of pregnancy, the PNM rate was 2·1%, which was only slightly higher than the overall hospital PNM rate for singleton pregnancies of 1·9% for the same period.

Table 1 shows the results of 24 h urinary oestriol estimations performed, as outlined above, in 455 patients (84·7%); the 354 (65·9%) with normal results had a PNM rate of 4%, whereas the 101 (18·8%) patients with one or more low oestriol values had a perinatal mortality rate of 22·7%.

Excluding the anencephalic fetuses, all of which had low values, the PNM rate associated with low oestriol excretion and polyhydramnios was 12% (11 of 89).

Table 1. Urinary oestriol excretion in patients with polyhydramnios

Oestriol result	Number of patients	Major congenital malformations	PNM rate
Normal	354	7·9%	4·0%
Low	101	28·7%	22·7%
Not done	82	44·4%	44·1%

PNM, perinatal mortality

Table 2 shows the fetal and maternal complications associated with polyhydramnios. In 248 pregnancies (46%), there were no associated fetal or placental abnormalities or maternal complications; the perinatal mortality rate in this group of patients with idiopathic polyhydramnios was 2·4%.

Associated maternal complications (Table 3)

Thirty-two women had pre-existing diabetes. Of the other 505 women, 383 (76%) had a glucose tolerance test (GTT) at 30–32 weeks (or earlier if indicated). The GTT was normal in 303 (60%), 70 women (14%) had gestational diabetes and 10 (2%) hypoglycaemia. In the 32 patients with pre-existing diabetes, all the infants survived and only one major congenital malformation (hypertrophic cardiomyopathy) occurred.

The PNM rate was 10% (7 of 70) in women with gestational diabetes and the causes of these deaths were major congenital malformations in three (one hydrocephalus, one left diaphragmatic hernia and lung sequestration, and one anencephalus), hypoxia in two (one due to rupture of the uterus and one unexplained), immaturity in one and sudden infant death on day 26 in one.

Table 2. Fetal and maternal complications* and the perinatal outcome in singleton pregnancies with polyhydramnios

	Alive	SB/NNB	PNM rate
Malformations (feta/placental)	37	59	61·4%
Pre-existing diabetes	32	—	0%
Gestational diabetes	63	7	10·0%
Pre-eclampsia	79	12	13·1%
Others	36	3	7.6%
None	242	6	2.4%
Total	464	73	13.6%

SB, stillbirth; NND, neonatal death, PNM, perinatal mortality; others, complications other than diabetes, pre-eclampsia or malformations

*The pregnancy in some patients was complicated both by fetal malformation and maternal complications; these patients appear twice in this table.

There were four additional non-lethal malformations in this group of patients giving a total rate of 10%: congenital heart malformation in one, ventricular septum defect and arthrogryposis in one, hydronephrosis in one, bilateral talipes in one.

During the same 10-year period 3·5% of the total hospital population had gestational diabetes with a PNM rate of 1·4%, and 0·3% had

Table 3. Associated maternal complications

Complications	No	(%)	Hospital rate (%)
Pre-existing			
Diabetes*	32	(5·9)	0·3
Renal problems:	9	(1·7)	0·8
Ig-A nephropathy	3		
Glomerulonephritis	3		
Pyelonephritis	1		
Renal insufficiency	1		
Renal transplant	1		
Thalassaemia trait	7		
beta	4		
alpha	3		
Epilepsy	4		
Crohn's disease	2		
Anorexia nervosa	1		
Coeliac disease	1		
Myotonic dystrophy	1		
Thyroid carcinoma	1		
Deep venous thrombosis	1	(0·2)	0·3
Pregnancy-related			
Pre-eclampsia*	91	(16·9)	6·6
Gestational diabetes*	70	(13·0)	3·5
Antepartum haemorrhage	29	(5·4)	3·1
Anaemia*	22	(4·0)	1·2
Urinary tract infection	15	(2·8)	0·8
Placenta praevia	14	(2·6)	1·2
Abruptio placentae	12	(2·2)	2·2
Rhesus-isoimmunization	2	(0·4)	0·5
Intrauterine infection	2	(0·4)	
Acute renal failure	2	(0·4)	
Cord prolapse	2	(0·4)	0·4
Amniotic fluid embolism	1	(0·2)	
Rupture of the uterus	1	(0·2)	

*Those conditions in which the frequency was highly significantly ($P < 0{\cdot}001$) increased compared to the total hospital populations.

pre-existing diabetes with a PNM rate of 3·1%. These figures indicate that the PNM rate is increased by a factor of 7 when gestational diabetes is complicated by polyhydramnios.

Pre-eclampsia complicated 91 pregnancies (17%) and was associated with a perinatal mortality rate of 13·1% (12 infants), the causes of these deaths were major congenital malformations in 10 and intrauterine infection in two. The hospital rate of pre-eclampsia, during the same period, was 6·6% with a PNM rate of 3·2%.

Renal problems were a pre-existing feature in nine women; IgA-nephropathy in three, glomerulnephritis in three of whom one required dialysis, pyelonephritis in one, renal insufficiency requiring dialysis in one and renal transplant in one

Other maternal diseases included: beta thalassaemia trait in four, alpha thalassaemia trait in three, epilepsy in four, Crohn's disease in two, and one each for anorexia nervosa, coeliac disease, myotonic dystrophy, thryroid carcinoma and deep venous thrombosis.

Two women developed intrauterine infection: one baby was born with hydrops fetalis and obstruction of the thoracic duct; the influenza B titre was elevated in maternal serum, cord serum and fetal pleural effusion fluid; this infant survived. The other patient developed syphilis during pregnancy and her baby survived but had hydrocephalus.

Other pregnancy-related complications were antepartum haemorrhage (29), anaemia (22), urinary tract infection (15), placenta praevia (14), placental abruption (12) and cord prolapse (2). One patient had amniotic fluid embolism during caesarean section. Another patient, para 5, suffered a ruptured uterus after induction of labour at 36·6 weeks when marked polyhydramnios was present; the infant was known to have bilateral hydronephrosis.

Two women developed acute renal failure probably secondary to ureteric compression by the pregnant uterus; in both, renal function returned to normal after delivery of the baby. These have been reported elsewhere (Carey *et al.* 1989).

Fetal malformations

A total of 155 congenital malformations occurred in 94 children (18%) and are listed in Table 4. The major group was central nervous system (CNS) abnormalities (31%) of which almost half (23 of 47) had anencephalus. Of all anencephalic infants, 82% were female and 78% growth retarded. All oestriol measurements recorded during these pregnancies showed extremely low results of between 2·4 and 12·1 μmol/24 h (0·7–3·5 mg 24 h). The PNM rate in the group with CNS abnormalities was high, 91·6%. After exclusion of all anencephalic infants, the PNM rate was 77·7%. Musculoskeletal malformations occurred in 11·5% with a PNM rate of 55·5%. Another important group was malformations of the digestive system (10%). Most infants in this group had some degee of gastrointestinal tract obstruction; although most were correctable by surgery, the PNM rate was 43·7%. Major cardiac malformations occurred in 9% with a PNM rate of 42·8%. Multiple system abnormalities occurred in 7% with a PNM rate of 63·6%. Hydrops fetalis occurred in 6% with a PNM rate of 90%. Cleft lip and palate occurred in 5% with a PNM rate of 50%, and limb abnormalities in 5%; these usually occurred in association with other major abnormalities. Upper alimentary tract abnormality, mainly atresia of the oesophagus, was diagnosed in 4% with a PNM rate of 16·6%; a tracheo-oesophageal fistula was present in three of the five infants. Abnormalities of the urinary system (4%), respiratory system (3%) and circulatory system (3%) had PNM rates respectively of 66·6%, 80% and 40%. A minority had eye (0·7%) and genital (0.7%) malformations.

To assess the frequency with which the most common fetal malformations were associated with polyhydramnios, the total hospital frequency of these malformations during the same period 1979 to 1988 was calculated (Table 5). Polyhydramnios was present in 71% where there was a large omphalocele or exomphalus (5 of 7), 68% with anencephalus (23 of 35), 63% with malrotation, volvulus or obstruction of the small bowel (5 of 8), 50% with Pierre Robin syndrome (3 of 6), 46% with oesophageal atresia (5 of 11), 42% with diaphragmatic hernia (8 of 19), 39% with hydrops fetalis (10 of 26), 27% with trisomy 18 (3 of 11), 17% with imperforate anus (2 of 12) and 11% with hydrocephalus (10 of 91).

Although ultrasound is helpful and indeed imperative to diagnose fetal malformations, in 18 children (20%) in this series the malformation was not recognized or recognizable by ultrasonography; these malformations were; cyst of the septum pellucidum (1), Pierre Robin syn-

Table 4. Fetal malformations* associated with polyhydramnios

Classification (International Classification of Disease 1988)	Number of infants			
	SB	NND	Alive	Total
1 Central nervous system: 30·7%				
Anencephalus	18	5	–	23
Hydrocephalus	2	5	1	8
Meningomyelocele	3	4	–	7
Hydrocephalus & spina bifida	–	1	1	2
Encephalocele	–	1	–	1
Microcephalus	–	1	–	1
Ruptured septum pellucidum	–	–	1	1
Cyst of septum pellucidum	–	–	1	1
Absent aqueduct	–	1	–	1
Teratoma medulla oblongata	–	1	–	1
Holoprosencephalus	1	–	–	1
	24	19	4	47
2 Musculoskeletal: 11·5%				
Diaphragmatic hernia	1	5	2	8
Pierre Robin syndrome	–	–	3	3
Skeletal abnormalities	–	2	1	3
Arthrogryposis	–	–	1	1
Camptomelic syndrome	–	1	–	1
Achondroplasia	–	–	1	1
Osteoporosis	1	–	–	1
	2	8	8	18
3. Digestive system 10·2%				
Omphalocele/exomphalus	1	1	3	5
Abdominal mass	–	1	1	2
Small bowel volvulus	–	–	2	2
Small bowel obstruction	–	–	2	2
Imperforate anus	1	1	–	2
Hiatus hernia	1	–	–	1
Malformation small bowel	–	–	1	1
Retropleural enteric cyst	–	1	–	1
	3	4	9	16
4 Heart: 8·9%				
Ventricular septal defect	–	2	3	5
Atrial septal defect	–	3	–	3
Common atrium	–	1	1	2
Hypertrophic cardiomyopathy	–	–	2	2
Transposition of great vessels	–	–	1	1
Pulmonary valve stenosis	–	–	1	1
	–	6	8	14
5 Multiple systems. 7·1%				
Trisomy 18	–	3	–	3
Trisomy 21	–	–	1	1
Trisomy 13	1	–	–	1
Triploidy	–	1	–	1
Cornelia de Lange syndrome	–	–	1	1
Beckwith syndrome	–	–	1	1
Robinow syndrome	–	–	1	1
Cytochrome-oxytose deficiency	–	1	–	1
Werdnig Hoffman syndrome	–	1	–	1
	1	6	4	11

Table 4 continued

Classification (International Classification of Disease 1988)	Number of infants			
	SB	NND	Alive	Total
6 Hydrops fetalis: 6·4%	1	8	1	10
7. Cleft palate and lip: 5·1%	1	3	4	8
8. Limbs: 4·5%				
Bilateral talipes	1	1	3	5
Congenital dislocation hips	–	–	1	1
Epiphysal dysplasia	–	1	–	1
	1	2	4	7
9. Upper alimentary tract: 3·9%				
Oesophageal atresia	–	1	4	5
Thoracic duct obstruction	–	–	1	1
	–	1	5	6
10 Urinary system: 3·9%				
Bilateral hydronephrosis	2	–	1	3
Polycystic kidneys	–	2	–	2
Vesicoureteric reflux	–	–	1	1
	2	2	2	6
11. Respiratory system: 3·2%				
Pulmonary hypoplasia	–	3	–	3
Agenesis right lung	–	–	1	1
Sequestration lung	–	1	–	1
	–	4	1	5
12 Circulatory system: 3·2%				
Patent ductus arteriosus	–	1	2	3
Hypoplasia aortic arch	–	1	–	1
Persistent fetal circulation	–	–	1	1
	–	2	3	5
13. Genital organs: 0·7%				
Hypoplasia external genitals	–	1	–	1
14. Eye: 0·7%				
Coloboma	–	–	1	1

*Some infants had more than one major malformation and appear in two or more categories. Thus, although there were 96 infants, the total shown in this table is 155

drome (2), Cornelia de Lange syndrome (1), oesophagel atresia (2), cleft palate (3), patent ductus arteriosus (2), persistent fetal circulation (1), hypertrophic cardiomyopathy (1), ventricular septal defect (2), skeletal malformation (1), talipes (2).

Placental abnormalities

Polyhydramnios was associated with a chorioangioma of the placenta in two patients both of whom developed acute polyhydramnios at 24 and 26 weeks respectively; the babies died from immaturity. Placenta accreta was diagnosed in one patient who had developed polyhydramnios at 27 weeks, laboured spontaneously at 28 weeks and developed massive postpartum haemorrhage requiring hysterectomy. Another woman developed polyhydramnios and severe pre-eclampsia at 26 weeks, and at 27 weeks she was delivered of a male infant weighing 974 g who died an hour after birth. The placenta weighted 970 g. Histology of the placenta showed the typical features of a hydatidiform mole. Chromoso-

Table 5. The frequency of polyhydramnios and the common major fetal malformations* with which it is associated

Major fetal malformation	Hospital rate in 51 022 singleton births (number)	Polyhydramnios	
		Number	(%)
Omphalocele/exomphalus	7	5	(71·4)
Anencephalus	35	23	(63 5)
Malrotation/volvulus/obstruction small bowel	8	5	(62·5)
Pierre Robin syndrome	6	3	(50·0)
Oesophageal atresia	11	5	(45·4)
Diaphragmatic hernia	19	8	(42·1)
Hydrops fetalis	26	10	(38·5)
Trisomy 18	11	3	(27 3)
Imperforate anus	12	2	(16 7)
Hydrocephalus	91	10	(10·9)

*Some infants had more than one malformation and appear in two or more categories.

mal analysis of the placenta and baby showed triploidy 69XXY. The infant had a cleft lip and palate and hypoplasia of the external genitalia. Only very rarely do triploid infants survive to be born after 28 weeks gestation (Wertelecki *et al.* 1976).

Discussion

There is no satisfactory explanation for most occurrences of polyhydramnios. It is recognized that polyhydramnios is frequently associated with diabetes, congenital and placental malformations and pre-eclampsia, which was confirmed in our series, the frequencies being diabetes (19%), congenital and placental malformations (18%) and pre-eclampsia (17%). The associated complications can partly explain the aetology, congenital malformations associated with polyhydramnios are principally central nervous system and gastrointestinal. tract abnormalities. Looking at the most common major malformations with which polyhydramnios was associated, we found that exomphalus, anencephalus, Pierre Robin syndrome, malrotation, volvulus and obstruction of the small bowel were associated with polyhydramnios in more than 50%, whereas oesophageal atresia was associated with polyhydramnios in 45%. This was a surprise finding as it is widely believed that polyhydramnios occurs much more often in these pregnancies. It is also noteworthy that despite the well recognized association of polyhydramnios and oesophageal atresia, the latter accounted for only 1% (5 of 537) in the present series Anencephalus represented 48% of infants with CNS abnormalities and it is suggested that these fetuses have both a decreased ability to swallow and polyuria secondary to lack of anti-diuretic hormone (ADH) (Naeye 1970). In the group with digestive disorders, which are commonly obstructive, impaired fetal swallowing is the probable cause of polyhydramnios.

Polyhydramnios was present in 50% of pregnancies complicated by Pierre Robin syndrome which is characterized by micrognathia associated with pseudomacroglossia, glossoptosis and high-arched or cleft palate. Posterior displacement of the attachment of the genioglossus muscle to the hypoplastic mandible prevents the normal anchorage of the tongue. Under the influence of gravity the tongue assumes a retruded position, obstructing the pharynx and resulting in impaired fetal swallowing

Polyhydramnios was present in 42% with diaphragmatic hernia. This is possibly explained by acute intestinal obstruction which may occur at any time in these patients Fetal polyuria can explain the occurrence of polyhydramnios in congenital heart malformations that cause increased cardiac output and renal perfusion (Kirshon 1989).

It was thought that fetal hyperglycaemia and associated polyuria accounted for polyhydramnios in patients with diabetes, but Van Otterlo *et al.* (1977) found no increase in urine output in such patients. In our series, polyhydramnios was associated with a higher PNM rate in gestational diabetes than in pre-existing diabetes (Table 2). The onset of polyhydramnios associated with diabetes was usually gradual with minor maternal symptoms.

When polyhydramnios was associated with a congenital malformation or placental abnormality (96 patients), there was a high PNM rate, 61·4%. This emphasizes the importance of antenatal diagnosis since knowledge of a lethal congenital malformation could influence the obstetric management. It is important, however, to realize the limitation of antenatal ultrasonography since in our series 20% of all malformations were not or could not be diagnosed with this investigation. Six of the 537 children were born with a chromosomal abnormality often associated with multiple malformations.

It is our opinion that every patient in whom polyhydramnios is diagnosed should have a complete investigation including expert ultrasonography, amniocentesis or cordocentesis for chromosomal analysis and glucose tolerance testing since congenital malformations, diabetes or pre-eclampsia were associated complications in 54% of all pregnancies with polyhydramnios in this series. Moreover oestriol assay identified a subgroup with a high PNM rate. It is crucial to identify these conditions since the result allows prognosis and future management to be determined. The frequency of gestational diabetes ($P < 0{\cdot}00001$), pre-eclampsia ($P < 0{\cdot}0001$) and pre-existing diabetes ($P < 0{\cdot}001$) were highly significantly increased in patients with polyhydramnios compared with the total hospital population.

The management of polyhydramnios is principally that of the underlying cause and usually is restricted to bed rest and tocolytic therapy if the patient has threatened preterm labour. Serial therapeutic amniocentesis is very occasionally required. If a congenital malformation is identified, it is essential to discuss the prognosis and further management with the paediatric physicians and surgeons before counselling the patient and her husband. Only a multidisciplinary approach will lead to optimal management of both infant and mother.

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Determinants of fetal and maternal atrial natriuretic peptide concentrations at delivery in man

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Summary. Matched maternal venous (MV), umbilical artery (UA) and umbilical vein (UV) concentrations of atrial natriuretic peptide [ANP] were measured in 36 normotensive women at term delivery (23 vaginal, 13 caesarean) and 17 non-pregnant women in the first half of the menstrual cycle. MV [ANP] at caesarean section was similar to that in non-pregnant women, but UA and UV [ANP] were higher ($P<0.01$ for both). UA, but not UV, [ANP] was markedly raised after vaginal delivery. Plasma concentrations of aldosterone [ALD] were measured in 16 of the matched sets of samples. No statistically significant association was found between [ANP] and [ALD] in either maternal or fetal samples. Neither maternal nor fetal [ANP] correlated with serum Na^+ or osmolality, haematocrit, blood pressure or heart rate.

Labour and delivery place major demands on the cardiovascular system of both mother and fetus. Hormones such as adrenaline, noradrenaline and angiotensin II (AT II) rise substantially in both the maternal and fetal circulations at vaginal delivery, but are much less influenced by elective caesarean section (Irestedt *et al.* 1982; Symonds & Broughton Pipkin 1980). The increased concentrations of catecholamines following normal delivery appear to be of relevance to the newborn in making the transition from intrauterine to extrauterine life (Lagercrantz *et al.* 1981).

Kikuchi *et al.* (1988) noted lower plasma concentrations of atrial natriuretic peptide ([ANP]) in three infants at birth by caesarean section than in seven vaginally-born infants, but did not attempt to determine any factor(s) which might have evoked the altered levels. Similarly, although Yamaji *et al* (1986) reported higher maternal [ANP] at vaginal delivery than in non-pregnant subjects, they did not study other possibly inter-related factors. We have therefore undertaken a study at normal term delivery, taking into account both some of those factors thought to influence [ANP] outside pregnancy (serum sodium and osmolality, volume of intravenous fluid administered) and those known to influence other peptide hormones at delivery (type and duration of labour, gestational age, birthweight and Apgar score at birth). Matched maternal venous, umbilical vein and artery blood samples were obtained from each mother and baby pair, to allow assessment of any placental influence on basal concentrations. The assay methods were specifically validated for use with pregnancy and neonatal plasma.

Subjects and methods

The study was approved by the hospital ethics

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committee. Blood samples were obtained at delivery from 36 women who had agreed to an extra venesection after earlier discussion with one of the authors; six women were primigravid. Samples were obtained from the antecubital vein in the late second stage of labour in 23 women and during elective caesarean section, as close as possible to delivery, in the other 13 women. The women were all delivered supine and had been in this position for at least 20 min. Matched samples of umbilical artery and vein blood were obtained in every instance, those from the artery and 32 from the vein being taken before delivery of the placenta; the remaining vein blood samples were taken within 1–2 min of placental delivery. The volume of fluid administered intravenously during labour was noted at the time of sampling. Eleven women received no intravenous fluids; 22 were given Hartmann's solution (three with added dextrose) and three were given dextrose, 5%. Fluids were given prophylactically in every instance. Intravenous preloading with 0·5–1 litre of Hartmann's solution immediately before epidural anaesthesia was routine. Samples were also obtained from 17 normal non-pregnant women recruited from departmental staff, students and midwives (mean age 29·3 SE 1·3 years) in the follicular phase of the menstrual cycle. None was using oral contraception. All subjects were taking unrestricted diets and denied recent drug ingestion. None had chronic hypertensive, metabolic or renal disease.

Samples were taken in pre-cooled syringes; the blood was immediately placed in chilled, silicone-coated glass tubes containing a mixture of EDTA (2 mg/ml blood) and aprotinin (Trasylol) (1000 kIU/ml blood) (see below). Additional samples of maternal and umbilical vein blood were placed in plain glass tubes for measurement of serum sodium and potassium concentrations and osmolality, and in EDTA tubes for measurement of haemoglobin concentration and haematocrit.

It was found in the course of assay validation prior to initiation of the study that a doubling of our normal inhibitor concentration was required for pregnancy and neonatal plasma. This requirement was especially apparent at high concentrations of ANP and was shown in a significant departure from unity of the slope of the calculated regression line for the association between measured [ANP] in the same blood sample divided between normal and twice normal inhibitor concentrations at sampling (slope = 0·827 ± 0·037, $P<0·001$). All samples were therefore taken into 'high concentration' inhibitor solution.

Extraction of ANP from plasma

This procedure was essentially that described by Thomsen *et al.* (1987). Samples (1·0 ml) were acidified by adding 3·0 ml of 2·9% acetic acid. The acidified samples were then applied to Sep Pak C_{18} cartridges (Waters Associates, Milford, Mass., USA) prewashed with 10 ml methanol and 10 ml distilled water. After washing with 20 ml distilled water, the ANP was eluted with 2·0 ml of an ethanol:water:acetic acid (80:20:4) solution. The eluates were reduced to dryness at 40° C under a stream of air and stored at −20° C until assayed. Recovery of added unlabelled peptide was 93% from maternal plasma and 89·3% from fetal plasma; assayed values were corrected for recovery. Doubling dilutions of reconstituted extracts assayed in parallel with the standard curve.

Radioimmunoassay of ANP

Samples were re-dissolved in 350 μl of 0·1 M phosphate assay buffer and assayed using a specific rabbit anti-α-ANP serum (Peninsula Laboratories, St. Helens, Merseyside, England) with incubation for 24 h at 4°C. Non-specific binding was assessed for the standard curve and for each sample. Iodine-125 labelled α-atrial natriuretic peptide (Amersham, Bucks, England) was added (100 μl) to all tubes, which were further incubated for 24 h at 4° C. Separation of the bound and free fractions was achieved using dextran coated charcoal. Doubling dilutions of reconstituted extracts assayed in parallel with the standard curve.

Sensitivity of the assay was 2 pg/tube with intra-assay and inter-assay variations of 6·4% (n = 10) and 13·3% (n = 41) respectively.

Other biochemical analysis

Serum electrolytes were measured using a Technicon SMA 560 Autoanalyser (Basingstoke, Hampshire, England) and osmolality by freezing point depression (Advanced Instruments freezing point osmometer, Partridge Green, Sussex, England). Haemoglobin concentrations and haematocrit were measured on a Coulter S

Plus IV counter (Luton, Bedfordshire, England). Plasma aldosterone (ALD) concentration was measured in all three samples from 16 patients (nine were delivered vaginally, and seven were sectioned) using a Coat-a-count kit (Diagnostic Products Corporation, Los Angeles, CA, USA).

Statistics

Values for [ANP] were not normally-distributed. Medians (with interquartiles in parentheses) have thus been given as a measure of central tendency and the Mann-Whitney U test used to test for the significance of difference between group medians. Normally-distributed data are given as mean (SE) values. Spearman's *rho* was used to assess correlation between variables unless otherwise indicated in the text.

Results

Table 1 summarizes some basal data concerning the pregnant women studied. Maternal heart rate at the time of sampling was slightly higher at caesarean section ($P<0{\cdot}05$), otherwise the basal data were very similar in the two delivery groups.

Data for the patients as a group are shown in Table 2. Overall, median maternal venous (MV) [ANP] was very similar to umbilical vein (UV) [ANP]. However, umbilical artery (UA)[ANP] was higher than UV[ANP] in 32 of the 36 infants ($P<0{\cdot}0001$). It was also significantly higher than the maternal value ($P<0{\cdot}003$). There was no correlation between MV[ANP] and either UV[ANP] (Fig. 1a, $r = -0{\cdot}22$, $P = 0{\cdot}2$) or UA[ANP] (Fig. 1b, $r = 0{\cdot}15$, $P>0{\cdot}3$) although UV and UA[ANP] themselves were strongly correlated (Pearson's $r = 0{\cdot}4858$, $P = 0{\cdot}003$; Fig. 2). The slope of the calculated regression line between the [ANP] in the two fetal samples differed significantly from unity (Fig. 2, broken line; $0{\cdot}35 \pm 0{\cdot}22$, $P<0{\cdot}01$).

Table 1. Some basal data concerning the pregnant women studied

	Vaginal delivery ($n = 23$)	Caesarean section ($n = 13$)
Age (years)	27·0 (1·0)	27·7 (1·6)
Gestational age (weeks)	39·7 (0·3)	39·0 (0·4)
Blood pressure before sampling (mm Hg)		
Systolic	119 3 (2·0)	122·7 (4·2)
Diastolic	71·7 (1·7)	72·5 (2·6)
Maternal heart rate before sampling (beats/min)	84·2 (1·4)	89·5 (2·6)
5 min Apgar score	9·7 (0·1)	9·5 (0·4)
Primiparae	3	3

* = The mean values differ significantly, $P<0{\cdot}05$). Results are means (SE) values.

Effect of mode of delivery

Of the 36 women, 20 had an uneventful, spontaneous vaginal delivery and 11 were delivered by elective caesarean section (the remaining five are detailed below). MV[ANP] was higher in the women delivered vaginally (Table 2; Fig 3) but this was not statistically significant ($P = 0{\cdot}058$). Median MV[ANP] was identical in the women delivered by elective caesarean section to the value found in the non-pregnant women in the first half of the cycle (median 33·5 pg/ml, interquartile range 22·0–40·5) but both UA and UV [ANP] were higher (Table 2; $P<0{\cdot}01$ for both). UA[ANP] was significantly higher after vaginal delivery than after birth by caesarean section ($P<0{\cdot}05$) but UV[ANP] was unchanged. Neither maternal nor fetal [ANP] correlated significantly with either the total duration of labour or the duration of the second stage of labour.

Three of the remaining five women had forceps deliveries; all had had epidurals and long second stages of labour (78–140 min). Maternal and fetal [ANP]s were within the range for unassisted vaginal deliveries. Two women were delivered by caesarean section for fetal distress in established labour; one had an [ANP] of 192 pg/ml, outside the range for elective section and above the 75th centile for vaginal delivery, but the other values were within the range for elective caesarean section.

Factors influencing MV[ANP]

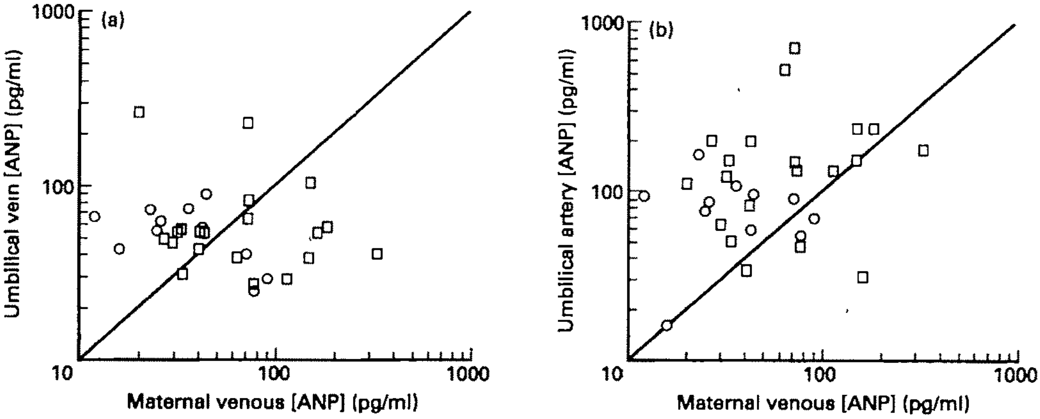
Neither age nor parity appeared to influence MV[ANP]. There was a fairly small range of systolic and diastolic blood pressures at delivery (Table 1) and no significant correlation was found between systolic or diastolic pressure or heart rate and MV[ANP]. Maternal median [ALD] was not significantly higher at vaginal delivery than at caesarean section but both

Table 2. Paired maternal and fetal concentrations of atrial natriuretic [ANP] and aldosterone [ALD] in all 36 deliveries studied, and also subdivided by mode of delivery. Note the very strong similarity in umbilical vein [ANP] regardless of mode of delivery

Variable	Maternal vein	Umbilical artery	Umbilical vein
Normal vaginal delivery (*n* = 20)			
Plasma [ANP] (pg/ml)	68·0 (33·3, 139·5)	141·0 (67·8, 199·5)	53·0 (38·5, 62·5)
Plasma [ALD] (ng/dl)	70·0 (58·3, 147·3)	138·5 (100·0, 245·8)	166·5 (91·8, 246·8)
Serum [Na) (mmol/l)	136·3 (0·5)	—	136·0 (0·6)
Serum osmolality (mos mol/kg)	273·3 (1·0)	—	275·7 (0·8)
Haematocrit (%)	36·6 (0·7)	—	46·8 (1·2)
Elective caesarean section (*n* = 11)			
Plasma [ANP] (pg/ml)	36·0 (23·0, 71·0)	85·0 (59·0, 95·0)	55·0 (40·0, 73·0)
Plasma [ALD] (ng/dl)	53·0 (41·5, 69·5)	59·0 (55·5, 107·0)	55·0 (50·0, 99·0)
Serum [Na$^+$] (mmol/l)	136·7 (0·4)	—	135·1 (0·8)
Serum osmolality (mos mol/kg)	276·9 (2·9)	—	281·8 (7·0)
Haematocrit (%)	34·9 (0·7)	—	44·9 (1·6)
Overall (*n* = 36)			
Plasma [ANP] (pg/ml)	43·5 (27·8, 87·8)	100·5 (64·5, 161·8)	54·0 (40·0, 71·8)
Plasma [ALD] (ng/dl)	60·5 (44·8, 79·0)	108·5 (60·3, 189.3)	119·5 (55·8, 190·0)
Serum [Na$^+$] (mmol/l)	136·5 (0·3)	—	135·7 (0·4)
Serum osmolality (mos mol/kg)	276·1 (1·7)	—	278·1 (2·2)
Haematocrit (%)	36·0 (0·5)	—	46·9 (0·9)

Results for [ANP] and [ALD] are median (interquartiles) values; the other data are given as mean (SE) values.

umbilical artery ($P<0·02$) and umbilical vein aldosterone (ALD) concentrations ($P<0·02$) were raised at vaginal delivery (Table 2). Maternal and fetal plasma ALD concentrations were highly significantly correlated with each other. There was a weak inverse association between overall MV[ANP] and ALD concentrations ($r = -0·362$, $P<0·1$) but this failed to reach formal statistical significance. Neither UA nor UV[ANP] were correlated with ALD concentrations in the same sample ($P>0·3$ for both). Furthermore, there was no correlation between MV[ANP] and maternal haematocrit, serum osmolality or sodium concentration at vaginal delivery. The volume of fluid administered during labour ranged between 0 and 2·5



(a) (b)

Figs. 1a and 1b. Plasma concentrations of atrial natriuretic peptide [ANP] in paired maternal and fetal samples obtained at delivery· (O) elective caesarean section; (□) normal vaginal delivery.

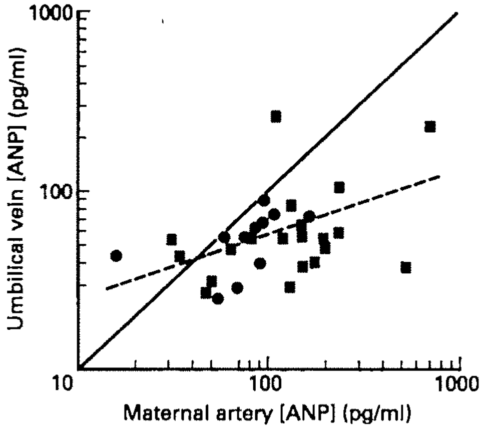


Fig. 2. Correlation ($P<0.003$) between umbilical artery (UA) and vein (UV) plasma concentrations of atrial natriuretic peptide (ANP) in samples obtained at delivery: (●) elective caesarean section; (■) normal vaginal delivery. The line of unity is shown together with the calculated linear regression line Log_{10} UV[ANP] = $1{\cdot}04 + 0{\cdot}36$ ($\log_{10}$ UA[ANP]).

litres; MV[ANP] was not influenced by the infusion volume administered at either vaginal delivery or caesarean section.

Factors influencing fetal [ANP]

A low Apgar score at 1 min was associated with increased UV[ANP] and UA[ANP], the association being significant for UV[ANP] ($P<0{\cdot}02$). Neonatal blood pressure was not measured. Umbilical artery [ANP] rose with increasing gestational age ($P<0{\cdot}05$) even over the narrow gestational age range studied (37–42 weeks) but UV[ANP] showed no such rise ($P>0{\cdot}4$). No correlations were found between UA or UV[ANP] and fetal haematocrit, serum osmolality or sodium concentration.

Discussion

Two factors of importance in regulating plasma [ANP] outside pregnancy are the central volume status, specifically as reflected in right atrial pressure (see Nicholls & Richards 1987) and heart rate (Tikkanen *et al.* 1985). Pregnancy is a state of volume expansion, but the increased plasma volume is normally accommodated in a dilated vasculature which includes the very vascular, low-resistance uterine circulation. Right atrial pressure is thus unchanged in pregnancy but heart rate is increased by some 10–15 beats/min at rest by the second trimester. Cusson *et al.* (1985) and Hirai *et al.* (1988) in cross-sectional studies reported increases of between 24 and 30% in mean [ANP] in women at varying stages of gestation, but Hatjis *et al.* (1989) found no such increase at term, and Rutherford *et al.* (1987) found that only one of seven women studied serially from the second trimester showed a rise in [ANP].

To our knowledge, this is the first study specifically to address the question of factors influencing maternal and fetal [ANF] at normal term delivery. Our finding of an identical MV[ANP] at elective caesarean section (basal) and in non-pregnant women confirms the lack of any major pregnancy effect *per se* on [ANP] at term. The observation that fluid volume administered did not influence [ANP] is interesting in the light of a very recently reported formal study also showing a failure of [ANP] to rise in late pregnancy during volume expansion to a level which increased non-pregnant [ANP] more than 60% (Hatjis *et al.* 1989). Castro *et al.* (1989) have also suggested that, in the pregnant rat, factors other than intravascular volume may influence [ANP].

Figure 3 shows a considerable widening of range of values of MV[ANP] at vaginal delivery compared with caesarean section. A marked increase in maternal AT II concentration occurs during vaginal, by comparison with abdominal, delivery (Symonds & Broughton Pipkin 1980), and the infusion of AT II between 28–32 weeks gestation is associated with a rise in [ANP] (Niesert *et al.* (1987). Maternal plasma noradrenaline also rises at vaginal delivery (Irestedt

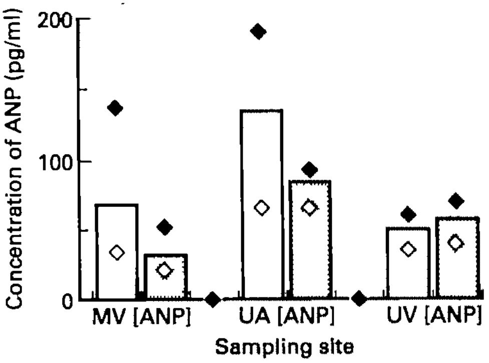


Fig. 3. Maternal venous (MV), umbilical artery (UA) and vein (UV) concentrations of atrial natriuretic peptides [ANP] at vaginal delivery (open) and elective caesarean section (shaded), The height of the column shows the median value, the 25th and 75th centile values are denoted by ◇ and ◆ respectively. Note the much greater variability of [ANP] following vaginal delivery.

et al. 1982). ANP inhibits the pressor response to AT II and noradrenaline in non-pregnant adults (Anderson *et al.* 1986; Uehlinger, Weidmann & Gnadinger 1985) and although some women become transiently hypertensive during labour, most do not. It may be that the increased vasoconstrictors found in labour stimulate the production or release of an appropriate antagonist. ANP has also been reported to inhibit AT II-induced aldosterone secretion in non-pregnant subjects (Anderson *et al.* 1986; Cuneo *et al.* 1987). The inverse association noted between MV[ANP] and MV[ALD] at delivery suggests that the same is true in pregnancy.

The raised UA[ANP] even at elective caesarean section was not unexpected in view of reports of increased abdominal aortic [ANP] in chronically-cannulated fetal lambs (Ross *et al.* 1987). Acute or chronic hypoxia is associated with raised plasma [ANP], plasma renin and renin substrate concentrations in human babies born by elective caesarean section (Tetlow & Broughton Pipkin 1983), in fetal lambs (Cheung & Brace 1988) and conscious rats (Winter *et al.* 1989; Gould & Goodman (1970). ANP has been reported to oppose the vasoconstrictor effect of AT II in the human placenta (Kingdom *et al.* 1989). Again, an interrelation between ANP and the renin-angiotensin system seems likely at this time. It is also possible that the chest 'squeeze' of the last few minutes of vaginal delivery evokes release of cardiac ANP following the transient elevation in trans-thoracic pressure.

Fetal lambs can respond to large increases in plasma volume and osmolality by increasing [ANP] (Ross *et al.* 1987; Miner, Cheung & Brace 1989); however, in our study there was no correlation between plasma osmolality or haematocrit and either UV[ANP] or UA[ANP]. The experimental increments evoked were large, and may thus not represent a physiological stimulus.

Specific ANP receptors of both low- and high-capacity have been demonstrated in human placentas (Hatjis & Grogan, 1988). Our observations of a marked and consistent UA[ANP]: UV[ANP] gradient, and those of Kikuchi *et al.* (1988), suggest strongly that the placenta is a major site of removal of ANP from the fetal circulation in women as it appears to be in sheep (Anwar *et al.* 1989). The observation that median UV[ANP] is very similar at elective caesarean section and at vaginal birth, in the face of a 60% rise in UA[ANP] at vaginal delivery and the deviation of the association UA:UV from 1, suggests a marked placental reserve capacity for the metabolism of ANP. Similar very high concentrations of placental peptidases for arginine vasopressin and oxytocin have been described (Rosenbloom *et al.* 1975; Thornton *et al.* 1988). Further evidence in support of this hypothesis was our finding of the need for increased concentrations of peptidase inhibitors in pregnancy and neonatal plasma (see above).

Thus both fetus and mother can acutely increase [ANP] during vaginal delivery, to concentrations only found in pathological states outside pregnancy, suggesting that in both it may have a role to play in regulating cardiovascular homeostasis. However, in this observational study no clear stimulatory factor could be identified; in particular, neither the volume of administered fluid nor maternal heart rate were associated with corresponding changes in [ANP]. Its role at delivery remains to be determined.

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The importance of the behavioural state in biophysical assessment of the term human fetus

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Summary. We have examined how the different behavioural states exhibited by 78 healthy fetuses at term influence the result of the non-stress test (NST) and biophysical profile score (BPS). In association with state 1F the average recording time to obtain a satisfactory NST and BPS was 27·0 and 26·3 min respectively, and 52·6% and 44·0% respectively failed to achieve a 'normal' result. In contrast, satisfactory results were always obtained in the two active states (2F and 4F), and the average time was 3–5 min. Mature fetuses spend on average one third of the time in state 1F, and knowledge of its characteristics is therefore important, for the interpretation of biophysical tests. Our results suggest that continuation of biophysical recording for at least 40 min is necessary before an unreactive NST or low BPS should be regarded as suspicious. We suggest that interpretation of the NST and BPS should be made in the light of knowledge of normal patterns of behavioural development rather than using an arbitrarily defined scoring system.

In recent years biophysical tests have gained increasing popularity for assessing fetal health in high risk pregnancy. The more widely used 'non-stress test' (NST) (Keegan & Paul 1980) assesses the presence of fetal heart rate (FHR) accelerations, while the biophysical profile score (BPS) (Manning *et al.* 1980) assesses a number of fetal variables, so improving the discriminative ability (Manning *et al.*, 1981, 1984, Baskett *et al.*, 1984). Neither test, however, makes allowance for the fetal behavioural state in the interpretation, although low scores are sometimes attributed anecdotally to fetal sleep.

Several years ago, the existence of fetal behavioural states, apparently similar to those exhibited by the newborn (Prechtl 1974), was demonstrated in fetuses beyond 36 weeks (Nijhuis *et al.*, 1982, 1984) They were therefore designated states 1F to 4F to distinguish them from postnatal states (different state variables are used in the newborn). Recently we have examined behaviour in a group of 80 healthy term fetuses and found that in most fetuses time is spent cycling between state 1F (characterized by absent eye movements, absent somatic movements except for the occasional startle, and narrow variability of the baseline heart rate without accelerations unless accompanying startles) and 2F (characterized by almost continuous eye movements, frequent bursts of somatic movements and wider baseline heart rate variability with frequent accelerations with movement). Episodes of a more active state, 4F, (characterized by almost continuous somatic and eye movements with a sustained fetal tachycardia) occurred infrequently and for 2–3% of the time,

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behaviour was indeterminate (Pillai & James 1990). We did not find a fourth state, 3F, described by other authors (Nijhuis *et al.*, 1982, 1984).

In neurological testing of the newborn, the importance of the behavioural state in interpretation is well-established (Prechtel 1974; Brazelton 1973; Dubowitz & Dubowitz 1981) In fetal life, the existence of activity/inactivity cycles is recognized and these are considered to influence cardiotocography and biophysical recordings, but their importance in the interpretation of such tests prenatally has not been stressed sufficiently The aim of the current study was to examine the influence of the fetal behavioural state on biophysical testing in a group of healthy fetuses at term.

Subjects and methods

Both primigravid and multigravid women, with low risk singleton gestations, attending the antenatal clinic at around 36 weeks gestation were invited to participate in a single study of fetal behaviour. Of the women recruited, 37 were primigravid and 41 multigravid. They were studied at between 36 and 42 weeks gestation. All studies were conducted by a single observer (M.P.) with the women in a quiet room in a comfortable semirecumbent position, we found a Parker Knoll reclining chair most suitable for this study.

Initial measurements of the fetal head, abdomen and amniotic fluid volume were made with ultrasound to confirm that these were low-risk pregnancies suitable for entry to the study. All 78 fetuses had head and abdominal measurements between the 5th and 95th centiles, and normal amniotic fluid volume (considered normal, if the largest pool measured in two perpendicular planes was at least 3 cm by 3 cm).

Fetal head, eye and upper limb movements were observed with one real-time ultrasound transducer (Siemens Sonoline SL1 with a 3·5 MHz transducer) while trunk and diaphragmatic movements were recorded with a second transducer (Toshiba SAL20A with a 3·5 MHz transducer). The fetal heart rate was simultaneously recorded ultrasonically with a standard fetal monitor (Hewlett Packard 8040A). With this equipment configuration there was minimal interference using all three transducers simultaneously All movements were recorded polygraphically at a paper speed of 3 cm/min, and intervals of each state were additionally recorded on video tape. Recordings were made between 0900 and 1800 h. These are the times when recordings are most likely to be undertaken in a clinical setting We have shown previously that there are no significant diurnal variations in behavioural states between these hours (Pillai & James 1990), whereas Patrick *et al.* (1982) noted a significant increase in fetal activity in the late evening.

Recording was continued long enough for episodes of the different behavioural states to be observed (usually for 90 to 110 min), except for two fetuses who remained in an active state for >120 min. The recordings were analysed for the distribution of the different behavioural states and their influence on the non-stress test and biophysical profile score determined for each fetus and for the whole group.

A satisfactory non-stress test result was defined as two or more FHR accelerations of >15 beats/min and >15 s duration (Keegan & Paul 1980), and a satisfactory biophysical profile result as a score of ≥8 out of 10 (all fetuses had normal amniotic fluid volume) in 30 min (Manning *et al.*, 1990).

Statistical significance between the times taken to achieve a satisfactory result in the different states was assessed with the paired *t*-test.

Approval for the study was obtained from the hospital's research and ethics committee.

Results

The total recorded time was 132.1 h. The distribution of the different states, illustrated in Table 1, shows that healthy mature fetuses spend about one third (31%) of the time in a quiescent state—1F (thought to correspond to quiet sleep in the newborn). The remaining time is predominantly taken up by state 2F (resembles REM sleep in the newborn) (57·1%), while a relatively small proportion of time is spent in a more active state 4F (8·9%).

Table 2 shows the average time taken to achieve satisfactory test results from the start of an episode of each of the three states. On most occasions a satisfactory result was obtained in 1F only after transition into one of the other states There were marked differences in the times taken to achieve a normal result in the three states (Table 2). The differences between 1F and 2F for both the non-stress and biophysical tests were highly significant ($P<0{\cdot}0001$) The differences between 2F and 4F on the biophysical test

Table 1. Distribution of fetal behavioural states in 78 health fetuses at term*

	Fetal state			
	1F	2F	4F	Indeterminate
No of episodes	117	134	20	21
No. of fetuses	76	77	19	21
Duration of episodes (min)				
Mean	21·87	33·73	37·16	3·21
(SD)	(8.68)	(17·56)	(19·60)	(6·25)
Maximum	38·0	94·0	122·0	20·0
Total	2459	4521	706	238
Percent	31·0	57·1	8·9	3·0

*Total recorded time = 132·1 h.

were also significant, but are not applicable to the non-stress test as state 4F is characterized by a sustained tachycardia which tends to obscure the baseline and hence accelerations. Performing such tests during state 1F considerably increases the chance of obtaining an unsatisfactory result. Figure 1 shows the biophysical profile scores achieved within 30 min of the onset of an episode of 1F in the 76 fetuses who manifested this state during their recording. Of these, 34 (44%) failed to achieve a satisfactory score (scored <8), and among the 42 fetuses who scored 'normally' 23 (55%) did so only because a change of state occurred well within the 30 min. Similarly, 40 fetuses (53%) would have failed a non-stress test when assessed for 30 min following the onset of state 1F.

Table 2. Time (in minutes) to achieve normal test results from start of each behavioural state in term fetuses

	Fetal state		
	1F	2F	4F
Biophysical profile			
Mean	26·29	5·22	3·13*
(SD)	(10·28)	(1·98)	(0·98)
Range	6–48	2–10	2–6
Non-stress test			
Mean	27·02	5·52	NA†
(SD)	(10·90)	(2·44)	NA
Range	6·5–48	3–15	NA

All values are in minutes.

NA = Not applicable, fetal heart rate characterized by a sustained tachycardia obscuring baseline (see text).

*For biophysical profile 1F *vs* 2F ($P<0\ 0001$) 2F *vs.* 4F ($P<0{\cdot}001$).

†For non-stress test 1F *vs* 2F ($P<0\ 0001$)

No episode of 1F lasted >38 min, and a normal result for both tests was always obtained within 10 min of transition out of state 1F, so that the longest time taken by any fetus to get a normal result for either test was 48 min.

We examined each biophysical variable in turn to see how it was influenced by the behavioural state.

Reactive fetal heart rate

The relation between the FHR pattern and behavioural state is shown in Table 2. In late pregnancy a high percentage of fetal movements are accompanied by FHR accelerations and therefore those fetuses who scored normally for movements invariably scored normally for heart rate and vice versa.

Movements

A normal biophysical profile score requires three movements or movement episodes in 30 min. This was always satisfied within a few minutes of 2F and seconds of 4F, however, in 1F this depended on the frequency of startles (a startle rate of at least 1 in 10 min would be necessary for a satisfactory score). The mean frequency of startles was 0·90/10 min (SD 0·86; range 0–4·28). Of 76 fetuses, 40 (53%) did not achieve the required rate in 1F. As well as wide inter-fetal variation, we also found considerable intra-fetal variability of the startle frequency between separate episodes of 1F.

Tone

This variable was always satisfied in 2F and 4F,

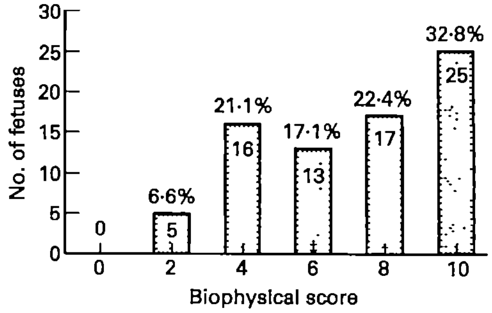

Fig. 1. Biophysical profile scores achieved within 30 min of the onset of an episode of state 1F in 76 fetuses.

Table 3. Fetal breathing and behavioural state in 78 fetuses

	Fetal state		
	1F	2 & 4F*	
FBM (%)			
Mean (SD)	23·6 (29·6)	38·9 (27·1)	$P<0·001$
Range	0–89·4	0–96·6	
No (%) with <30 s of sustained FBM in given state	32 (42·1)	4 (5·1)	$P<0·001$

Total time = 132·1 h
*States 2 and 4F were combined because state 4F occurred in very few recordings.
FBM = fetal breathing movement

however, it was the variable least likely to be satisfied in 1F. The reason for this is that it requires not only startles to be present in 1F but that the startles last long enough and are sufficiently vigorous to produce rapid limb extension with more gradual return to flexion, or opening of the hand with return to a closed fist formation (Manning *et al.*, 1990). This was not satisfied in 67 (88%) of the fetuses during 1F.

Fetal breathing

Table 3 shows the distribution of fetal breathing with each behavioural state. In quantifying breathing we included all episodes containing at least four consecutive breaths and lasting ≥5 s, and we excluded all apnoeic intervals with no breathing movements for ≥6 s. There was wide individual fetal variation, with two fetuses having no breathing at all during >100 min of continuous observation, and three fetuses breathing for over 86% of their observation time. More breathing occurred in the active states than in 1F, and in particular, fetuses are much less likely to sustain 30 s of continuous breathing during 1F. These differences were highly significant ($P<0·0001$).

The biophysical profile requires at least 30 s of sustained fetal breathing in 30 min; 42% of the fetuses failed to satisfy this during state 1F.

Amniotic fluid volume

This was a prerequisite of normality for entry into the study. It was the only variable not influenced by the behavioural state and therefore the minimum biophysical score obtained on any occasion was 2/10.

Neonatal outcome

All babies were born between 2 and 17 days after study, and all birthweights were between the 5th and 95th centile for gestational age (mean 3466·3 g SD 406 g) (Gairdner & Pearson 1971, 1985). All had 1 and 5 min Apgar scores >5 and >7 respectively. One newborn required admission to the neonatal unit for investigation of pyrexia which resolved spontaneously, but otherwise the only neonatal problem was moderate jaundice in three babies.

Discussion

Biophysical tests are commonly used for assessing fetal health and have been widely investigated in high risk pregnancy. However, there are no data regarding the rate of false positive results in low-risk pregnancy.

Our study suggests that interpretation may be greatly enhanced by understanding how normal patterns of fetal behaviour at term may influence the results obtained. The existence of fetal behavioural states has been established for nearly a decade (Nijhuis *et al.* 1982). Healthy fetuses at term spend about one third of their time in a quiescent state, 1F (Table 1) (Pillai & James 1990*a*) and intervals of this state generally last 20–30 min and rarely for as long as 40 min. We have shown that if biophysical recording happens to start in the first few minutes of one of these episodes an unsatisfactory result is frequently obtained. On the basis of these findings we suggest that recordings should be continued for at least 40 min before an unreactive non-stress test or low biophysical profile score should necessarily be regarded as abnormal. We would advocate continuing the test in this way rather than repeating the test later, in order to avoid the chance occurrence of repeating the test in state 1F, and also because it gives a quicker result which is important if there is acute fetal compromise.

Fetal quiescence has often been taken as an ominous finding. Although this may be true if unduly prolonged, alternating quiet and active behavioural cycles may be a much more important feature of an intact nervous system than any particular biophysical test.

As far as biophysical assessment of the fetus is concerned, episodes of normal 'fetal quiet sleep' (state 1F) greatly increase the necessary recording time, and may result in iatrogenic intervention if the normal characteristics of this state are not appreciated by those interpreting the test. Clearly there is scope for examining the characteristics of this state more closely (for example features not currently scored for such as fetal mouthing movements (Pillai & James 1990*b*) with the aim of learning to differentiate 'quiet but healthy' fetus from the 'quiet and compromized' fetus.

Fetal heart rate recording has been around for a long time, and yet its value is still in debate (Steer & Carter 1989). This is not surprising when interpretation was derived on an empirical basis and introduced before investigating the physiological mechanisms which underlie development of fetal heart rate patterns.

Although our findings are of relevance only to term fetuses, it is likely that knowledge of normal behavioural patterns at earlier gestations might be equally important to interpretation of biophysical tests applied to the preterm fetus. Our data emphasize the importance of understanding the physiological mechanisms which underlie the normal fetal heart rate pattern and fetal behaviour in interpretation of these biophysical tests at term rather than using an arbitrarily defined scoring system.

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The epithelial changes associated with squamous cell carcinoma of the vulva: a review of the clinical, histological and viral findings in 78 women

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Summary. Seventy-eight excised specimens of squamous cell carcinoma of the vulva were reviewed retrospectively for the presence of lichen sclerosus or vulvar intraepithelial neoplasia (VIN) at sites proximal to the tumour or more distant. Lichen sclerosus was evident in 61% and VIN alone in 31%. VIN III (differentiated) was associated with over 50% of the specimens with lichen sclerosus. HPV 16 was found in six of the 11 VIN lesions, investigated but in none of the six with lichen sclerosus.

Squamous cell carcinoma of the vulva is a relatively uncommon malignancy, occurring mainly in women of ≥60 years of age. Successful management depends largely on early diagnosis, as lesions with a histological depth of invasion of ≤1 mm carry an excellent prognosis (Wilkinson 1985). It is therefore essential to recognize and treat appropriately those epithelial abnormalities of the vulva that may have a premalignant potential. Previously these precursor states have been cited in the literature as carcinoma in situ and atypical hyperplastic dystrophy (Buscema *et al.* 1980; Zaino *et al.* 1982). According to the refined classification system adopted by the International Society for the Study of Vulvar Disease (Friedrich, 1976; Wilkinson *et al.* 1986) these two premalignant states should now be considered as vulvar intraepithelial neoplasia (VIN). VIN III is defined as full-thickness atypia with disordered maturation and atypical mitoses (Fig. 1). More recently, a differentiated type of VIN III has been defined as atypia limited to the lower third of the epithelium along with almost normal maturation more superficially (Fig. 2). Table 1 summarizes the current classification of vulvar tumours and vulvar non-neoplastic disorders as recommended by the International Society of Gynecological Pathologists.

In this article, we describe the clinical features, histopathological and viral characteristics observed in the skin adjacent to the lesion in our series of squamous cell carcinoma of the vulva in an attempt to define those conditions that may be associated with a risk of malignant disease

Subjects and methods

This was a retrospective study based on 78 women with squamous cell carcinoma of the vulva seen at our hospital between 1976 and the beginning of 1987. The analysis involves the histological features of the skin immediately adjacent to the carcinoma and more distant. It is accepted that epithelial abnormalities occur in the proximity of squamous cell carcinoma of the vulva (Buscema *et al.* 1980; Zaino *et al.* 1982). The features that were recorded included the presence or absence of a definite band of hyalinization in the upper dermis, cellular atypia and

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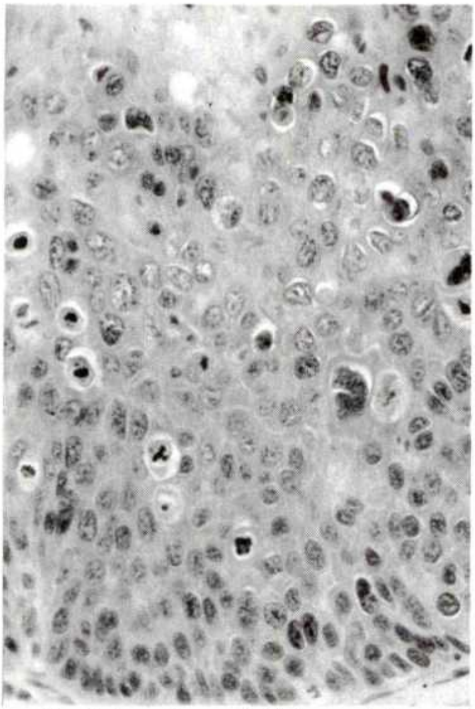

Fig. 1. Vulvar intraepithelial neoplasia undifferentiated type: full-thickness atypia with striking nuclear abnormalities and abnormal mitosis (×320).

epithelial hyperplasia. Furthermore, 18 of these specimens were investigated for human papilloma virus infection (HPV).

DNA preparations cleaved with PstI restriction endonuclease were electrophoresed in duplicate, 1% agarose denatured and transferred to nitrocellulose membranes. The membranes were hybridized as described Barasso *et al.* (1987). The duplicate membranes were dehybridized and run for two further cycles of hybridization and washing, using two other sets of 32 P-labeled DNA probes. Probes applied successively were HPV type 16 DNA or a mixture of type 6 and 11 DNAs, type 18, 31 or 33 DNA and finally type 39 or 42 DNA. Hybridizations were done at 60° C for high-stringency conditions or at 42° C for low-stringency conditions.

Results

Histological findings

Table 2 summarizes these findings together with a classification based on that recommended by the International Society for the Study of Vulvar Disease in 1976 with modification in 1983 and 1986 (Friedrich 1976; Wilkinson *et al.* 1986). Cellular atypia confined to the lower part of the epidermis with almost normal maturation as described by Abell & Gosling (1961) is now referred to as VIN III (differentiated) (Wilkinson *et al.* 1986).

Clinical findings

Table 3 summarizes the clinical findings in the 48 women with squamous cell carcinoma of the vulva associated with lichen sclerosus. In this table induration refers to a hardening or thickening of the skin and underlying tissue, an erosion represents partial or total loss of epidermis with preservation of the underlying dermis and ulceration is full loss of epidermis with some loss of dermis.

Table 4 summarizes the clinical findings of the 24 women with squamous cell carcinoma associated with VIN III (undifferentiated).

The six women in the idiopathic group, with neither VIN III associated lesion nor lichen sclerosus, all presented clinically with tumours, five on the labia minora and one on the labia majora. The age range was 58–70 years (mean 62·6, mode 63 years).

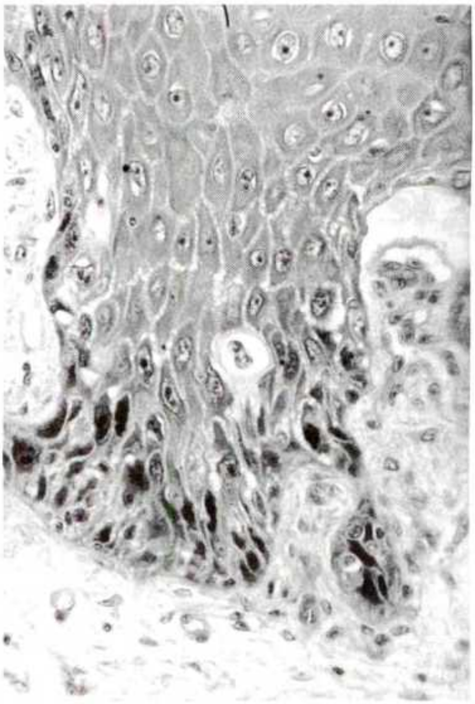

Fig. 2. Vulvar intraepithelial neoplasia differentiated type: nuclear atypia, abnormal mitosis are confined to the basal area which contrast with almost normal maturation up-above (×320).

Table 1. Classification of vulvar dystrophies and tumours as interpreted from the report of the ISSVD terminology committee*

Non-Neoplastic epithelial disorders
Lichen sclerosus
Squamous cell hyperplasia
Other dermatoses e.g psoriasis, lichen planus ..

Neoplastic epithelial disorders
VIN I — Mild dysplasia
VIN II — Moderate dysplasia
VIN III (Undifferentiated), severe dysplasia with full-thickness atypia VIN III (differentiated) atypia confined to basal layers, presence of keratin pearls in the rete pegs

* Wilkinson *et al.* (1986).
ISSVD = International Society for the Study of Vulvar Disease VIN = Vulvar intraepithelia neoplasia

Virological findings

Table 5 summarizes the virological results in 18 women investigated for HPV.

Discussion

From our results, as shown in Table 2, there appear to be two main precursor states for invasive carcinoma of the vulva: lichen sclerosus and VIN III (differentiated). Lichen sclerosus was found in 61% of the women studied and 50% of them also had VIN III (differentiated). VIN III (undifferentiated) was not associated with lichen sclerosus in any of our patients. Epithelial hyperplasia was noted in 12 of our 48 women with lichen sclerosus. This hyperplasia was either superimposed on the lichen sclerosus or at more distant sites. At sites where there is hyperplasia, the histological features of lichen sclerosus may be indistinct or even absent (Hart *et al.* 1975). This phenomenon may explain why the reported proportion with lichen sclerosus has been lower in other studies in which hyperplastic changes were present in >50% of the women with carcinoma of the vulva, because these studies reported lichen sclerosus only when it was present in the immediate vicinity of the cancer (Buscema *et al.* 1980; Zaino *et al.* 1982). Indeed, in our experience we have seen patients with clinically extensive lichen sclerosus who had no histological evidence of this in the tissue excised. This anomaly has been noted previously (Hewitt *et al.* 1987). Our results are in line with those of Wallace (1971), who found lichen sclerosus in 61% of 85 patients with carcinoma of the vulva, usually in association with a hyperplastic epithelium, whether dysplastic or not.

In seven specimens of invasive carcinoma associated with lichen sclerosus, there was no evidence of HPV DNA sequences, whereas in carcinoma associated with VIN III (undifferentiated) lesions, HPV DNA sequences were detected in 7 of 11 specimens (Table 5). These results suggest that HPV does not have a role in inducing malignant changes in lichen sclerosus.

Malignant change is stated to occur in <5% of women with lichen sclerosus who are under long-term review and treatment (Wallace 1971; Hart *et al.* 1975). Our histological findings of a 61% association of squamous cell carcinoma with lichen sclerosus seems extremely high. Forty-three of our patients presented with their malignant lesion and had undiagnosed lichen sclerosus and therefore had not received treatment. The remaining four had had lichen sclerosus diagnosed previously but had received inadequate treatment and follow-up. This might suggest that undiagnosed and untreated lichen sclerosus carries a greater risk of malignant progression and that treatment may alter outcome. This hypothesis requires further research. The age range for these lichen sclerosus patients was 20 to 94 years (mode 76 years). There were two women <40 years of age who had had lichen sclerosus since childhood Interestingly, all the malignant lesions that developed in the lichen

Table 2. Histological findings in adjacent skin in 78 women with squamous cell carcinoma of the vulva

Histology	Number (%) of women		Classification
Full thickness atypia	24	(31)	VIN III (undifferentiated)
Upper dermal band of hyalinization	8	(10)	Lichen sclerosus
Upper dermal hyalinization + basal atypia	28	(36)	Lichen sclerosus plus VIN III (differentiated)
Upper dermal hyalinization + hyperplasia	12	(15)	Lichen sclerosus plus squamous hyperplasia
No other abnormality	6	(8)	Idiopathic

Table 3. Clinical findings in 48 women with squamous cell carcinoma (SCC) of the vulva associated with lichen sclerosus

Clinical features	Number of women
Tumour	22
Hyperkeratotic plaque	4
Induration + erosion	7
Hyperkeratotic plaque + erosion	7
Ulceration	6
Erosion	2
Site of SCC	
Clitoris	15
Clitoris + labia minora	2
Labia minora	28
Labia minora + majora	3
Age (years)	
Range	20–94
Mean	68.7
Mode	76

sclerosus group (Table 3) arose exclusively on the labia minora or clitoris, a finding already recorded by Wallace (1971). This may be related to the fact that genital lichen sclerosus is restricted largely to the inner part of the vulva, and the outer part of the labia majora is less often affected (Wallace 1971).

VIN III (undifferentiated) was present in 24 women (31%). This proportion agrees closely with those of previous studies (Buscema *et al.* 1980; Zaino *et al.* 1982), as does our finding that invasive carcinomas associated with VIN III (undifferentiated) occurred mainly in those older than 50 (Abell & Gosling, 1961; Buscema *et al.* 1980; Crum *et al.* 1984). Clinically, the lesions consist of sharply defined plaques, sometimes multiple, with a tumour or induration indicating the invasive area. This clinical presentation is that previously classified as Bowen's disease (Gross *et al.* 1987).

Table 4. Clinical findings in adjacent skin in 24 women with squamous cell carcinoma (SCC) of the vulva associated with VIN III (undifferentiated)

Clinical features	Number of women
Tumour	12
Hyperkeratotic plaque	3
Ulceration	1
Erythroplasia alone	6
Erythroplasia plus hyperkeratotic plaque	2
Site of SCC	
Multifocal	7
Clitoris	2
Labia minora	8
Labia majora	3
Perineal	3
Perianal	1
Age (years)	
Range	33–89
Mean	64.3
Mode (bimodal)	51, 79

In one woman the clinical features were quite different. This 34-year-old patient presented with an extensive form of VIN III Bowenoid papulosis of the type reported by Bergeron *et al.* (1987). The lesions were pigmented, wart-like and involved the entire surface of the vulva and the perianal area. An ulcer on the right labium majus proved to be an area of invasive carcinoma. Bowen's disease and Bowenoid papulosis, despite their identical histology, have been described as separate clinical entities, Bowen's disease affects an older age group, around 50 years of age, and appears most commonly as a solitary, sharply defined plaque-like lesion (Abell & Gosling 1971; Gross *et al.* 1987), whereas Bowenoid papulosis affects a population around 30 years of age (Wade *et al.* 1979; Crum *et al.* 1984). Clinically, lesions are usually multiple, multicentric and polymorphous, characterized by papular lesions more suggestive of flat condyloma than of Bowen's disease. Furthermore, the risk of malignant progression in these two conditions is quite different. Malignant change is more common in the Bowen's group, but this is probably related to age (Crum *et al.* 1984). Indeed, in most affected patients, Bowenoid papulosis has a benign, short- and intermediate-term evolution, and may dis-

Table 5. Virological findings in 18 women with squamous cell carcinoma (SCC) of the vulva

	Squamous cell carcinoma associated with	
Probe	Lichen sclerosus ($n = 7$)	VIN III (undifferentiated) ($n = 11$)
HPV 16	0	6
HPV 18	0	0
HPV 31	0	1
HPV 33	0	0
HPV X*	0	0
HPV 6	0	0

* undetermined type.
HPV = human papilloma virus.

appear spontaneously (Wade *et al.* 1979; Crum *et al.* 1984). The very few examples of invasive carcinoma reported in young patients occurred in those with extensive Bowenoid papulosis or in those who were immuno-compromised (Buscema *et al.* 1980; Bergeron *et al.* 1987). The current classification attempts to discourage the use of the eponymous terms, Bowen's disease and Bowenoid papulosis, and prefers all these to be referred to as VIN III. However, from our study, it appears that older women with plaque-like lesions have a higher risk of malignant progression than those younger women with extensive lesions. Indeed, despite the current steep rise in the prevalence of VIN III lesions in the younger population, there is no corresponding increase in the occurrence of vulvar carcinoma (Crum *et al.* 1984). This suggests either a long latent phase or, alternatively, that current therapy is an effective prophylaxis. It would seem that the term VIN III alone is insufficient. It describes the histological features accurately but fails to separate the two distinct clinical groups, Bowen's disease and Bowenoid papulosis. This distinction is important as the prognosis for each is probably very different.

In the HPV-related lesions, importance must be attached to the clinical features and the age of the patient. The lesions at risk are well defined plaques, sometimes multifocal previously described as Bowen's disease. In our series, 83% of these lesions occurred in women over the age of 50. Only one patient in our series, a young woman, had extensive, poorly defined lesions. This is extremely unusual, as these patients normally follow a benign course.

The idiopathic group encompassed six patients Two of them were reported to have had lichen sclerosus, but at the time of presentation there was no clinical evidence of this nor, on later removal of the tumour, any histological changes to support this diagnosis. Clinically, all six presented with large tumours.

Finally, carcinomas, either associated with HPV-related lesions or associated with lichen sclerosus, are closely related to age, occurring most often in women of over 60 years of age.

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Outcome of a second pregnancy after a previous elective caesarean section

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Summary. At Queen Charlotte's Maternity Hospital from 1980 to 1987, 195 women had a trial of scar in their second ongoing pregnancy, having been delivered previously by elective caesarean section. Overall 154 (79%) achieved a vaginal delivery. Patients who went into spontaneous labour had a significantly better chance of being delivered vaginally than those who were induced. A past history of early pregnancy loss had no influence on the outcome, nor was outcome compromised in the group of patients whose elective caesarean section had taken place before 32 weeks gestation.

In the latest report on maternal mortality published by the Department of Health (1989), caesarean section still carries a three-fold risk of mortality compared with vaginal delivery. The death rate from caesarean section is falling but the overall use of caesarean section is rising, and this is worrying

Obstetricians have performed increasing numbers of elective caesarean sections in recent years, often on primigravid women, for reasons such as intrauterine growth retardation and breech presentation. Before allowing such a trend to become accepted practice the obstetrician needs to be aware of the effect of the caesarean section on the outcome of future pregnancies. At the present time such information is lacking.

This study describes 195 women managed at Queen Charlotte's Maternity Hospital between 1980 and 1987 who underwent trial of scar for their second delivery after a previous delivery by elective caesarean section before labour.

Subjects and methods

For this retrospective study, information was extracted from the hospital records. The records of all women who gave birth to a second baby between 1980 and 1987 inclusive were screened to identify those whose first ongoing pregnancy was ended by an elective caesarean section after 26 weeks and who had never been in labour. Women for whom induction of labour had failed were not included. Fourteen sets of notes were untraceable, leaving 353 records for analysis.

Of the 353 women, 220 (62%) had been delivered of their first babies in Queen Charlotte's Hospital and their details were obtained directly from the notes. Information on the other 133 (38%) women was derived from correspondence with the hospital where the first birth occurred and from the woman herself. In a few instances (<2%) no reply was received from the original hospital so details were obtained only from the woman. Only those who had clearly had an elective caesarean section were included in the analysis.

Results

Of the original 353 women in the study 158 were again delivered by elective caesarean section. This left 195 women with singleton pregnancies and cephalic presentations who were allowed a

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Table 1. Outcome of labour in 195 women who had a trial of scar in their second pregnancy, 1980-1987

Outcome of labour	1980	1982	1984	1986	Total
Vaginal delivery	34 (77%)	27 (75%)	46 (84%)	47 (78%)	154 (79%)
Emergency caesarean section	10 (23%)	9 (25%)	9 (16%)	13 (22%)	41 (21%)

trial of scar; 154 (79%) were delivered vaginally and 41 (21%) had an emergency caesarean section (Table 1). Eighty-seven (56%) of those delivered vaginally gave birth spontaneously and 67 (44%) were assisted.

The mean age of the women who were delivered vaginally was 29·7 years (SD 4·94) and the mean age of those who had an emergency caesarean section was 29·1 years (SD 4·98). The difference between the two means is not statistically significant.

Table 2 relates the mode of onset of labour to subsequent outcome. Spontaneous labour occurred in 137 women of whom 118 (86%) were delivered vaginally. Of the 58 women who were induced, 36 (62%) were delivered vaginally. The occurrence of vaginal delivery in the two groups was significantly different (χ^2 with Yates' correction = 12·8; $P \leq 0{\cdot}001$). The odds ratio of a second delivery by caesarean section was 3·8 (95% CI 1·9 to 7·8) for women whose labour was induced compared with those whose labour started spontaneously.

Table 3 shows the outcome of the second pregnancy in relation to the gestational age at the time of the first abdominal delivery. Of the original 353 women in the study, 35 had their first elective section before 32 completed weeks and 17 of them had a repeat elective caesarean section, leaving 22 women who were permitted trial by scar. Of these 22 women 21 (95%) were delivered vaginally.

In Table 4 the outcome of trial of scar is examined in relation to previous early pregnancy loss When the overall ratio of vaginal delivery to emergency caesarean section is taken into account, previous pregnancy loss has no bearing on the mode of delivery.

Infant birthweight in relation to mode of delivery has also been examined (Table 5). With the possible exception of those babies weighing either <2·5 or >4·1 kg, birthweight had no effect on the outcome of labour. One stillbirth resulted from the single instance of scar dehiscence in a woman whose labour was induced with two prostaglandin pessaries. Mention was not always made in the notes as to whether the lower segment scar was palpated after delivery. There were, however, no other recorded instances of scar dehiscence nor were there any episodes of post-partum haemorrhage of which scar dehiscence might have been the cause. There was one other intrapartum death, of a fetus with hydrocephaly and spina bifida, but no neonatal deaths.

A total of 142 women had epidural analgesia. Of these 107 (75%) were delivered vaginally and 35 (25%) underwent emergency caesarean section.

Discussion

The caesarean section rate in England and Wales has been increasing steadily since 1970 (Department of Health 1989) and shows no sign of slackening. Indeed, as the expectations of pregnancy outcome amongst the community continue to rise, so will the pressure on obstetricians to resort to caesarean section, particularly when the fetus is considered to be 'high-risk'. In some cases the woman will be nulliparous and her caesarean section will be elective. What then of her prospects for subsequent vaginal delivery?

Table 2. Outcome of labour in relation to the mode of onset in 195 women who had a trial of scar in their second pregnancy

	Mode of delivery	
Onset of labour	Vaginal (n = 154)	Emergency CS (n = 41)
Spontaneous		
Augmented	15	5
Non-augmented	103	14
Total	118 (86%)	19 (14%)
Induced		
ARM only	1	1
ARM plus oxytocin	5	1
PG pessaries only	20	12
PG pessaries plus oxytocin	10	8
Total	36 (62%)	22 (38%)

PG = prostaglandin.
ARM = artificial rupture of membranes.
CS = caesarean section.

Table 3. Outcome of trial of scar in relation to gestational age (completed weeks) at time of first delivery by elective caesarean section in 195 women

Gestational age at first delivery (weeks)	*n*	Mode of second delivery: Vaginal	Mode of second delivery: Caesarean section
27–30	14	14 (100%)	0 (0%)
31–34	24	14 (58%)	10 (42%)
35–38	70	52 (74%)	18 (26%)
39–42	87	74 (85%)	13 (15%)
Total	195	154 (79%)	41 (21%)

In the present study 195 such women were permitted a trial of scar and 154 (79%) were delivered vaginally. This compares favourably with recent studies (Meier & Porreco 1982, Nielsen & Hokegard 1984; Eglinton *et al.* 1984; Graham 1984; Jarrell *et al.* 1985; Ngu & Quinn 1985, and Paul *et al.* 1985), comprising for the most part women who were in labour at the time of their initial caesarean section. In contrast, none of our patients had ever been in labour. Molloy *et al.* (1987) reviewed 1781 consecutive women who had had one caesarean section and found the subsequent vaginal delivery rate was 91%. This rate, in a large series, is above average but may have been influenced by the fact that 1009 of their women had had a previous vaginal delivery, which facilitates subsequent vaginal delivery (Whiteside *et al.* 1983). Previous vaginal delivery may also be the reason why Molloy *et al.* (1987) noted a lower than expected emergency caesarean section rate of 7·7% in those women who had had a previous elective caesarean section. For similar reasons we considered whether a history of induced abortion or miscarriage might influence the outcome of labour, but found no evidence among our patients to suggest that it did.

Induction and oxytocic augmentation of labour remain controversial topics in women undergoing trial of scar. Our results point to a significantly better prospect for vaginal delivery if labour was allowed to start spontaneously, regardless of the method of induction. This is not to say that augmentation with oxytocin is contraindicated since, when used in a judicious manner, oxytocin appears to be safe (Horenstein *et al.* 1984). The single uterine scar dehiscence in our series occurred in a woman induced with prostaglandin only and resulted in fetal death.

One of the areas where the practice of caesarean section is expanding rapidly is for the birth of the extremely preterm fetus, when hypoxia in labour or birth trauma may lead to intracranial haemorrhage with subsequent cerebral palsy. Pressure on the obstetrician, often from the prospective parents in addition to the paediatrician, together with the ever lengthening shadow of litigation, mean that increasing numbers of babies between 26 and 32 weeks are being born electively by caesarean section. With no proper lower segment at this stage, the standard type operation may prove difficult, and sometimes unusual (T shaped) or even classical incisions are used to achieve delivery. It is reassuring that of the small number of women in our series who underwent their first caesarean section before 32 completed weeks, of 22 who had a trial of scar 21 achieved vaginal delivery. A recent review by Pinion & Mowat (1988) highlights some of the problems encountered after preterm caesarean

Table 4. Numbers of women with a previous early pregnancy loss in relation to outcome of trial of scar

Pregnancy loss	*n*	Vaginal delivery	Caesarean section
At <14 weeks			
Miscarriage	34	28 (82%)	6 (18%)
Induced abortion	23	18 (78%)	5 (22%)
At 14–27 weeks			
Miscarriage	9	8 (89%)	1 (11%)
Induced abortion	4	4 (100%)	0 (0%)
Total	70	58 (79%)	12 (21%)

Table 5. Outcome of trial of scar in relation to birth weight in 195 women

Birthweight	Vaginal delivery	Caesarean section
2·0–2·5	6 (54%)	5 (46%)
2·6–3·5	104 (83%)	21 (17%)
≥3·6	44 (74%)	15 (26%)
Total	154 (79%)	41 (21%)

section and advocates prospective studies in this field.

Seitchik & Rao (1982) found a significantly reduced rate of vaginal delivery after a previous caesarean section in women with babies weighing over 3500 g and this is what one would expect. At the other end of the scale, although our numbers are very small, it is interesting that of the 11 babies with birthweight <2500 g, five were born by emergency caesarean section, almost certainly reflecting the concern of the clinician for the fetal outcome.

What conclusions then can be drawn from this relatively small study? It would seem that for the woman whose first baby is born by elective caesarean section for a non-recurring indication, there is on average a 4 out of 5 chance of her achieving a vaginal delivery next time around, provided labour is allowed to begin spontaneously and provided the baby weighs between 2·5 kg and 4·0 kg. Even with induction 2 of 3 women should achieve vaginal delivery This information provides a measure of reassurance for the obstetrician as well as for the woman for whom the possibility of a vaginal delivery is important.

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Maternal haematocrit in labour is related to fetal cord pH at delivery

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Abstract

Objective—To determine whether a correlation exists between maternal haematocrit in labour and umbilical cord pH values at delivery.
Design—An observational study.
Setting—The delivery suite.
Subjects—200 pregnant women in labour.
Main outcome measures—Umbilical artery and vein blood pH values.
Results—A statistically significant inverse correlation was observed between maternal haematocrit levels during labour and umbilical vein pH ($r = -0{\cdot}22$; $P = 0{\cdot}001$) and umbilical artery pH ($r = -0{\cdot}18$; $P = 0{\cdot}008$) at delivery.
Conclusions—Although an inverse correlation does appear to exist between maternal haematocrit and cord pH values, it is unlikely that this weak association will prove to be of clinical value in the management of labour.

By tradition, obstetricians have directed much attention towards the detection and prevention of anaemia in pregnancy. In recent years, however, there has been a growing awareness that high maternal haemoglobin and haematocrit levels should also give cause for concern. Pregnancy-induced hypertension, preterm delivery, intrauterine growth retardation, low Apgar scores, perinatal death and placental infarction all occur with increased frequency in pregnant women with haemoglobin values in the upper range of normal (Murphy *et al.* 1986, Garn *et al.* 1981; Mau 1977; Naeye 1977).

The present study was designed therefore to assess whether a relation exists between maternal haematocrit levels and fetal acid-base status at delivery.

Subjects and methods

The study was undertaken in the labour ward of the Northern General Hospital, Sheffield, between March and July 1989.

Eligible women (those in labour with a mature, singleton fetus in a cephalic presentation) were approached shortly after admission to the delivery suite. After informed consent had been obtained and before the administration of any intravenous fluid during labour, 5 ml of maternal venous blood was withdrawn for haematocrit estimation. Haematocrit was measured with an H5000 analyser (Technicon, New York, USA].

At delivery, the umbilical cord was doubly clamped and blood samples were withdrawn anaerobically from the umbilical vessels into heparinized syringes. The pH was measured within 15 min using a 945 AVL automatic blood gas analyser (AVL, Schaffhausen, Switzerland) without prior knowledge of the maternal haematocrit.

Information regarding the course of labour, including maternal haematocrit, cord vessel pH, fetal birthweight and Apgar scores was recorded.

Statistical analysis used a Statsgraphics soft-

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ware package (Statsgraphics Corps, Maryland, USA). For the purposes of statistical analysis the pH values were expressed in terms of hydrogen ion concentration.

Results

In 200 women, pH values from both the umbilical artery and vein were obtained following delivery (another 29 were excluded from the present analysis as attempts to obtain samples from both vessels were unsuccessful).

The mean gestational age at delivery was 39·7 weeks (range 36–42), and the mean interval between the collection of the maternal blood sample and delivery was 6·4 h (range 1–20).

The mean maternal haematocrit was 35·3% (SD 3·7%). The mean umbilical vein pH was 7·30 (SD 0·06), and the mean umbilical artery pH was 7·20 (SD 0·08).

The relation between cord pH and maternal haematocrit was explored using regression analysis A significant inverse correlation between umbilical vein pH and maternal haematocrit was obtained ($r = -0{\cdot}22$, $P = 0{\cdot}001$, Fig. 1). R squared (the proportion of variance explained by the haematocrit) was 5%. There was a similar relation beween umbilical artery pH and maternal haematocrit ($r = -0{\cdot}18$, $P = 0{\cdot}008$). Significant inverse correlations were also seen when the analysis was confined to primigravidae, women delivered spontaneously and after the exclusion of those who smoked or who were hypertensive.

The strongest inverse correlation between umbilical vein blood pH and maternal haematocrit was found when the analysis was confined to the 92 women who had received no form of intravenous fluid therapy during labour ($r = -0{\cdot}31$, $P = 0{\cdot}003$, $R^2 = 9{\cdot}3\%$, Fig. 2).

The umbilical artery pH was ≥1 SD below the mean in seven of the 20 women who had haematocrit values of ≥40%.

A direct correlation was noted between birthweight and umbilical vein pH ($r = 0{\cdot}14$, $P = 0{\cdot}03$), but no such relation was demonstrable between cord artery pH and birthweight. There was a trend towards a reciprocal relation between fetal birthweight and maternal haematocrit which was not statistically significant ($r = -0{\cdot}12$, $P = 0{\cdot}07$).

No statistically significant correlation was found between cord pH values and the duration of the first and second stages of labour, in this sample of 200 women.

Discussion

The reported range of mean cord pH values is wide, but those presented here are compatible with the results of other large studies (Sykes *et al.* 1982; Huisjes & Aarnoudse, 1979).

Criteria for the diagnosis of fetal acidosis at delivery are arbitrary, but common definitions include pH values below the 10th centile or ≥1 SD below the mean. It has been suggested that the use of Apgar scores to assess neonatal condition at birth should be supplemented by cord pH measurement in order to characterize more fully the degree of fetal asphyxia (Sykes *et*

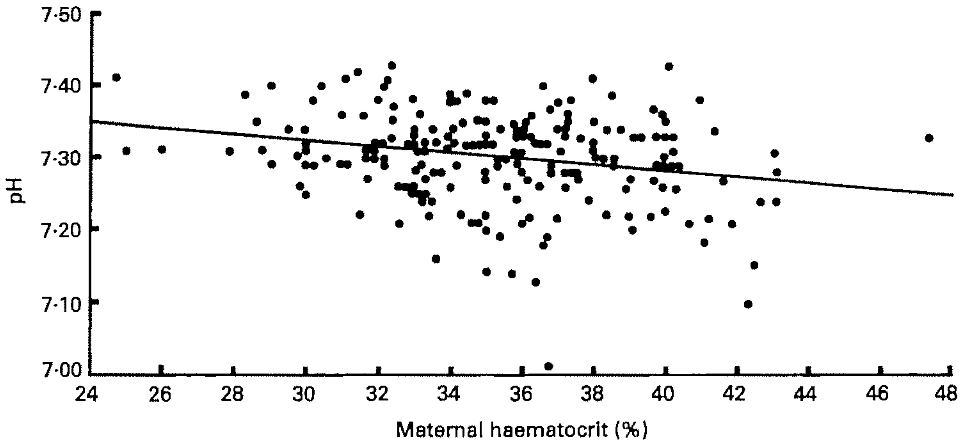

Fig. 1. Plot of umbilical vein pH at delivery against maternal haematocrit in labour (200 observations)

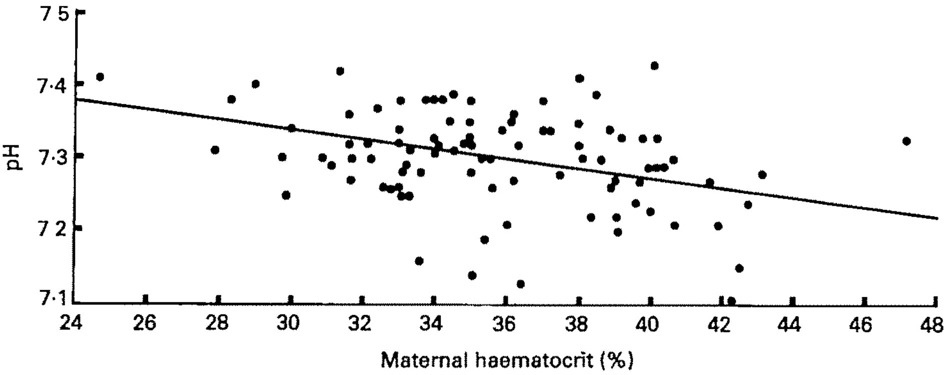

Fig. 2. Plot of umbilical vein pH at delivery against maternal haematocrit in patients not receiving intravenous fluid infusion during labour (92 observations).

al. 1982; Silverman *et al.* 1985) and to provide an index of the quality of perinatal care (Eskes *et al.* 1983).

Present day fetal monitoring techniques are intended to detect fetal acidosis during labour in order that delivery may be expedited and any prolonged asphyxial insult avoided. It is convenient to relate the severity of asphyxia to the degree of acidosis, but there is actually no single factor which will characterize fully the severity of an asphyxial insult (Myers 1972). Not all acidotic babies are depressed at birth, and not all depressed babies are acidotic, and clinical outcome is undoubtedly influenced by many variables including the duration and degree of asphyxia and acidosis and the maturity and nutritional status of the infant. In animal experiments, however, the more depressed the pH, the more probable is the development of brain injury and the more difficult resuscitation becomes (Myers 1972). In humans, acidotic babies are more likely to have early neurological morbidity, (Huisjes & Aarnoudse 1979; Low *et al.* 1977) although their long-term prognosis remains to be established.

It has been reported that fetal pH at delivery may be influenced by many variables such as length of labour and mode of delivery, but Yudkin *et al.* (1987) concluded that 'many important factors remain to be identified'. The results of the present study have indicated that maternal haematocrit may indeed be one of these factors.

An inverse correlation between maternal haemoglobin and birthweight has been reported previously (Sagen *et al.* 1984), as has the relation between fetal birthweight and umbilical vein, but not artery, pH levels (Yudkin *et al.* 1987). This latter observation may be due to the fact that the vein blood pH is a more direct reflection of placental function than that of the artery blood.

In the present study the strength of the inverse correlation between haematocrit and pH was improved by excluding all women who had received intravenous fluid during labour, and thereby all those given intravenous oxytocin or epidural analgesia (factors which in themselves may modify pH).

The observed relation between maternal haematocrit and cord pH possibly reflects the fact that adequate plasma volume expansion is the hallmark of successful pregnancy Where such change has been suboptimal, the resulting high haematocrit may be therefore merely an indicator of a poor quality pregnancy For example, both cigarette smoking and pregnancy-induced hypertension may produce an elevation in haemoglobin, and may also be associated with an increased occurrence of obstetric morbidity. It is interesting, however, that the relation between high haemoglobin and poor outcome persists even after controlling for these variables (Garn *et al* 1981).

The haematocrit could also be important in its own right, since it is the major determinant of whole blood viscosity. High levels may therefore impair placental perfusion. It remains to be seen whether plasma volume expansion during labour will improve the acid-base status of infants born to mothers with high venous haematocrits.

Although a high maternal haematocrit (>40%) may be a risk factor for fetal acidosis in labour, the relation may not be strong enough to be of any great clinical value.

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Carbon dioxide laser treatment for vulval papillomatosis (vulvodynia)

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Summary. Genital papillomatosis accompanied by distressing vulval symptoms is often termed vulvodynia. Common presenting symptoms are vulvar burning, pruritus and dyspareunia. Sixteen patients with vulval papillomatosis (vulvodynia) have been treated by carbon dioxide laser therapy over a 4-year period. Initial responses at 6 weeks appeared encouraging but with follow-up it became apparent that the relapse rate was high, with a mean symptom-free interval of 4·6 months. Of the 16 patients treated, only three remain symptom free. In view of our findings, we recommend that laser therapy should not be offered as a primary procedure, if at all, for patients with vulval papillomatosis.

Vulval disease is common but the aetiology of many vulval conditions is poorly understood and treatment is, of necessity, mostly empirical. Symptoms can be distressing and embarrassing and help may be sought only reluctantly.

The discovery of the significance of koilocytosis and the increased ability to detect human papillomavirus (HPV) has allowed the aetiology of many conditions to be attributed to this virus. There has been an increase in macroscopic genital papillomatosis which has been paralleled by an increase in subclinical papillomatosis accompanied by distressing vulval symptoms, often termed vulvodynia.

Many patients attending our clinic complaining of vulval burning have marked aceto-white epithelium on vulvoscopy and koilocytosis alone on histological examination of biopsy specimens. Although at present the significance of these features is unclear, it is possible that they may represent an atypical reaction to the presence of HPV. Since the carbon dioxide laser was introduced into gynaecological practice *in the* mid-1970s, it has been increasingly used to treat a variety of vulval conditions. We have been using laser therapy for patients with vulvodynia, to provide a nonmutilating treatment for this distressing condition.

Patients and methods

During a 4-year period, 16 patients have been diagnosed as having vulval papillomatosis (vulvodynia) and have been treated with the carbon dioxide laser at the Birmingham and Midland Hospital for Women. Other causes for their symptoms, such as chronic candidiasis, cyclic vulvitis and vestibulitis were excluded by detailed interview and examination. The pathological specimens have been reported by one of us (T.P.R). Patient details have been transcribed from the case notes. All the patients were initially seen in the colposcopy clinic and

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no patient has been lost to follow-up. Relapsed disease has been classified as symptomatic if the patient's original symptoms recurred following laser therapy.

Results

The mean age of the 16 patients was 36 years (range 19–66), with a peak prevalence in the fourth decade. Twelve women were premenopausal, one was postmenopausal and three had had hysterectomies.

Vulval pain was the commonest symptom (11 patients, 69%). Other common symptoms were vulval pruritus in nine (56%) and dyspareunia and postcoital pain in nine (56%). Infrequent symptoms were vaginal discharge in two patients, vulval swelling and abnormal vaginal bleeding in one patient each. Patients often had two or more symptoms. The mean duration of symptoms was 41 months (range 6–96 months).

All patients were assessed colposcopically with full examination of the lower genital tract. Various appearances were noted. Ten patients had acetowhitening; 13 had evidence of warts (macroscopic in six and microvilli in seven); two had erythematous and one had hypertrophic changes. The lesions were multifocal in nine patients, confluent in five and unifocal in only two.

Six patients had previously had abnormal cytology. Two of these had been treated for cervical intraepithelial neoplasia, one had HPV changes on cervical biopsy and one had cervical carcinoma.

All patients underwent diagnostic biopsy: ten of these were performed under local anaesthesia using a Keyes punch biopsy knife and six had biopsies under general anaesthesia. Single biopsy was performed in 12 patients and multiple biopsy in four. All specimens showed koilocytosis and some also showed other features of HPV infection, for example papillomatosis and hyperkeratosis, with no other pathological processes.

All 16 patients have been treated with superficial laser therapy by experienced personnel using a carbon dioxide laser in superpulse or chopped mode, down to the second surgical plane (Reid 1985a). Paraffin gauze dressings were applied postoperatively and removed within 24 h. The treated area was irrigated with normal saline, dried with a hairdrier and silver sulphadiazine cream was applied at least twice daily. Two patients developed labial adhesions which required division under general anaesthesia. Another patient, surprisingly, conceived within 6 weeks postoperatively!

Patients were followed in the colposcopy clinic. Ten patients (63%) reported symptomatic relief at the 6-week follow-up examination. The relief was shortlived in most of them, only three (19%) remain symptom free at the censor date 21,7 and 40 months after laser therapy. The mean symptom-free interval was 4·6 months.

Discussion

In the western world, we are experiencing an epidemic of sexually transmitted HPV infections (Department of Health, 1989). Most affected patients develop condylomas after an incubation period. Many of these lesions regress spontaneously or with simple therapy (Reid 1985b). In some women the lesions become chronic and refractory to conventional therapy. Vulval papillomatosis (vulvodynia) is increasingly being diagnosed by the advent of vulvoscopy and directed biopsy. Differential diagnosis includes cyclic vulvitis and vestibulitis, with which it may overlap or coexist (McKay 1989). Vulval papillomatosis is symptomatic, commonly presenting with vulval pain, pruritus and dyspareunia. Various treatments have been described, all characterized by a poor response or mutilation of the vulval structure and function. There have been favourable reports on the use of laser therapy in such patients (Baggish 1980).

Before treatment with laser a biopsy is essential to confirm the diagnosis and exclude malignancy or vulval intraepithelial neoplasia. The affected areas are treated under colposcopic guidance in order to minimize the area lasered and to assess the depth of destruction. The initial response at 6 weeks appeared encouraging but with follow-up it became apparent that the relapse rate was high, with a mean duration to relapse of 4.6 months. Of the 16 patients treated only three remain symptom free.

In view of our findings we recommend that laser should not be offered as a primary procedure, if at all, for patients with vulval papillomatosis. If the operation is offered, surgeons must counsel the patient and her partner adequately and be certain that the extent and severity of the condition justify contemplation of this operation. It must not be assumed that the technical sophistication of laser treatment guarantees a successful outcome. The symptoms are distressing to the patient and it remains important to continue assessment of new treatments that preserve vulval structure and function but eradicate symptomatology associated with vulval papillomatosis.

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Persistent fetal sinus bradycardia associated with maternal anti-Ro antibodies. Case report

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Case report

A 29-year-old woman had had two uneventful pregnancies both of which had resulted in the normal birth of healthy babies with normal heart rates. Nine years after the second delivery the patient developed polyarthralgia and an erythematous malar rash. Serology at that time was positive for antinuclear factor (titre 1 in 256) and anti-Ro antibodies but negative for antiphospholipid antibodies. Systemic lupus erythematosus was suspected and the symptoms were controlled with a non-steroidal anti-inflammatory agent (ibuprofen 400 mg twice daily).

One year later she attended the antenatal clinic after 12 weeks amenorrhoea in her third pregnancy. The disease had been quiescent for 6 months and she had stopped all treatment just before conception. Her serology was unchanged and VDRL testing was negative. Ultrasonography at 18 weeks revealed an appropriately sized, apparently normal fetus.

The pregnancy continued uneventfully until 32 weeks when a mild exacerbation of the lupus erythematosus developed. At this time a fetal bradycardia of 90 beats/min was discovered on routine auscultation. Complete heart block was suspected but cardiotocography, which confirmed the bradycardia, showed a normally reactive heart rate pattern (Fig. 1). Ultrasonography revealed a well-grown active fetus with normal amniotic fluid volume and no malformation. Detailed fetal echocardiography demonstrated synchronous atrial and ventricular systoles, suggestive of a sinus bradycardia, but no structural defect and no evidence of heart failure. Fetal umbilical artery blood velocity, measured with continuous-wave Doppler, was normal throughout systole and diastole.

Prednisolone (10 mg oral daily) was commenced and the lupus flare was quickly suppressed. Although the bradycardia persisted, fetal activity was maintained and cardiotocograms remained reactive. The pregnancy was allowed to proceed and despite the bradycardia fetal growth continued satisfactorily and cardiac failure did not develop.

At 37 weeks the patient developed a severe cutaneous vasculitis. Although the fetus remained active and the cardiotocograms reactive, delivery was expedited to avoid the potential complications of a possible concomitant placental vasculopathy. The cervix was favourable for induction and the vertex was presenting Amniotomy was performed, a fetal scalp electrode applied and continuous fetal heart rate monitoring commenced. The fetal heart rate was low at 90 beats/min, but the pattern was reactive throughout. Labour progressed uneventfully to a normal birth of a healthy female baby with a heart rate of 80 beats/min and Apgar scores of 7 and 8 at 1 and 5 min respectively.

The child made good progess Neonatal electrocardiography showed a sinus bradycardia (82 beats/min) with normal P waves, P-R interval and QRS complexes. Echocardiography again revealed no structural abnormality and thyroid function was likewise normal. The baby was discharged on the seventh day of life. On review 4 months later she remained well with a heart rate of 90 beats/min

Discussion

Fetal bradycardia often reflects severe fetal

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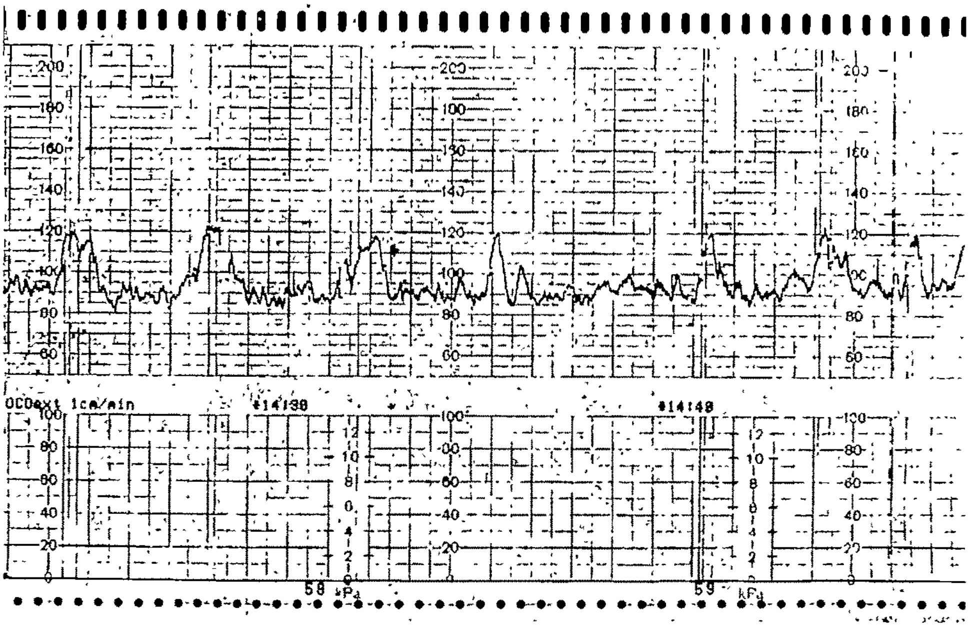

Fig. 1. Fetal heart rate trace showing baseline bradycardia but normal variability

hypoxia but this seemed to be unlikely in the presence of normal fetal activity and heart rate variability, and other causes were therefore sought. Fetal bradycardia due to complete heart block is a well recognized feature of pregnancies complicated by maternal anti-Ro antibodies (Scott *et al.* 1983), but again the variable heart rate pattern went against this diagnosis, which is characterized by a fixed rate bradycardia (Beall & Paul 1986) By demonstrating atrio-ventricular synchrony, fetal echocardiography suggested that the arrhythmia was atrial in origin (Allan *et al.* 1984).

Fetal echocardiography was also used to help exclude any structural cardiac malformations, a common finding with fetal arrhythmia (Crawford *et al.* 1985), and to look for early evidence of cardiac failure (Kleinman *et al.* 1983). Other conditions reported in association with fetal bradyarrhythmias include severe hydrocephalus (Katz *et al.* 1986), fetal panhypopituitarism (Marsh *et al.* 1987) and congenital hypothyroidism (Kaplan 1985), but these have been excluded in this case. The expected diagnosis of sinus bradycardia was eventually confirmed by neonatal electrocardiography, thereby excluding other varieties of profound congenital atrial bradyarrhythmias such as sino-atrial block (Shenker *et al.* 1979). Nevertheless, the cause of this arrhythmia remains obscure. One could speculate that the sino-atrial node had been damaged by endocardial fibroelastosis, the process responsible for the destruction of the lower conducting system in cases of isolated congenital heart block associated with maternal autoimmune disease (Ho *et al.* 1986). This seems unlikely however in the absence of any abnormality of the P wave or P-R interval on ECG. Perhaps this case merely represents a casual association of maternal anti-Ro antibody and a benign idiopathic sinus bradycardia. Regardless it serves to demonstrate that not all fetal bradycardias found in association with maternal connective tissue disease are due to heart block Antenatal determination of the type of arrhythmia present is important for two reasons. Firstly, the prognosis for the various bradycardias differs greatly (Crawford *et al.* 1985) and prior knowledge of the probable diagnosis allows the obstetrician and paediatrician to make any necessary special arrangements well in advance of delivery; babies with congenital heart block, for instance, occasionally need pacemaker insertion on the first day of life (Pinskey *et al.* 1982) and not all neonatal units are sufficiently well equipped to deal with this emergency. Secondly, fetuses in sinus rhythm can be monitored by cardiotocography and vaginal delivery contemplated, as in our patient. In contrast heart block renders the interpretation of heart rate patterns impossible and caesarean section is generally advocated (Stewart *et al.* 1983), although Beall & Paul (1986) have suggested that intermittent fetal scalp blood pH measurement may be a satisfactory alternative.

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Cardiac rhabdomyoma as a marker for the prenatal detection of tuberous sclerosis. Case report

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Case report

The 32-year-old patient had a brother affected by cardiopathy (ventricular septal defect). Her father had an ill-defined cardiopathy and died at the age of 63. One healthy daughter had been born spontaneously at term.

She had routine ultrasound scans at 10, 23 and 31 weeks gestation. The last one showed a fetal cardiomegaly and a marked echodense thickening (22–13mm), involving mainly the sub-epicardium and the endocardium of a large part of the wall of the right ventricle and atrium (Fig. 1–2).

At 32 weeks, cerebral ventricle asymmetry with dilation of the left lateral ventricle could also be seen (Fig. 3).

In the following weeks a multifocal increase in the cardiac echo-dense tumour was noted. Subendocardial localizations in the left ventricle and some localizations in the right and left papillary muscles appeared, and there was a marked reduction of the right ventricular cavity. The cardiac great vessels appeared to be affected by two tumours: one was affecting a flap of the semilunar aortic valve, and the other the supravalvular region of the pulmonary artery.

The presence of multiple new tumours led to the diagnosis of cardiac rhabdomyoma, which together with cerebral involvement suggested tuberous sclerosis.

The male child was born spontaneously at 39 weeks gestation with a birthweight of 2·900 kg and Apgar scores of 9 and 10 at 1 and 5 min respectively. His condition was excellent with no cyanosis or cardiac arrhythmia. There was a harsh systolic murmur and he was pink and reactive. The respiratory rate was 55/min and the heart rate 100 beats/min, he had normal femoral pulses and normal arterial pressure.

A neonatal heart scan confirmed the prenatal picture and aortic valvular stenosis was assessed by echodoppler. The electrocardiogram showed a subepicardiac lesion of the right ventricle. The cerebral echograph demonstrated the presence of a left subperiventricular rounded mass of 1·5 cm, which was lifting up the floor of the left lateral ventricle, partially obstructing Monro's foramen and causing dilation of the ventricle. (Fig. 4).

These findings were confirmed by cerebral CT scan, which also defined the presence of other tumours: bilateral subependymal, right frontal and left occipital cortical. The renal echograph was normal. After the diagnosis of tuberous sclerosis, the parents were further investigated (dermatology, ophthalmology, cerebral scan, renal echography). Renal echography showed the presence of an angiolipoma typical of tuberous sclerosis in the mother. Paediatric and echographic follow-up was carefully planned and at the age of 4 months, achromic patches appeared and hypertensive crises began. At 6 months neuropsychomotor development and haemodynamic compensation were within normal limits.

Echocardiography showed a reduction in size of all cardiac tumours and the continuous Doppler confirmed a progressive reduction (at pres-

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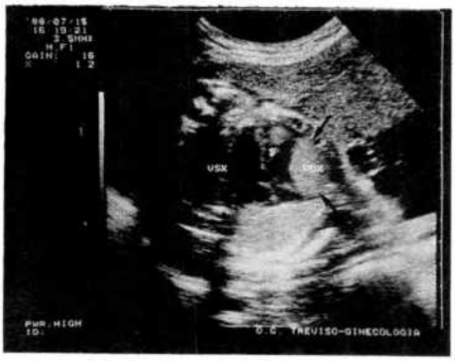

Fig. 1. Four chamber view of fetal heart: ecodense structure on right ventricular and atrial wall (arrows) (31 weeks gestation).

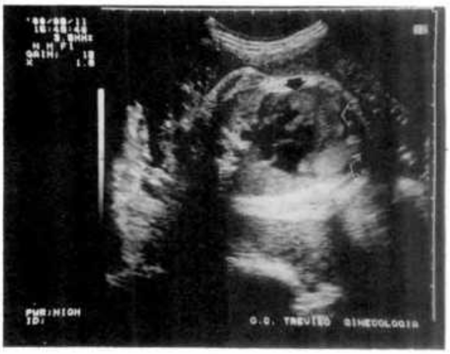

Fig. 2. Ecodense structure on left papillary muscle (solid arrow), endocardium, epicardium (open arrows).

ent almost complete) of the aortic obstruction. Cerebral echography showed no change in ventricular dilation and in the dimensions of the swellings, and revealed the presence of a new small sub-ependymal neoformation. The follow-up programme is being continued.

Discussion

The first case of tuberous sclerosis in a newborn infant was described by Von Recklinghausen (1862) and although more than a century has passed since then, there are still not very much data on this disease. Tuberous sclerosis is a rare hereditary genetic disease (its prevalence, reported in different studies, varies from 1 in 15 000 to in 50 000). It is autosomal dominant with a penetrance of 90–95% and variable expression (Hunt *et al.* 1984). It is traditionally characterized by the triad of epilepsy, mental retardation and skin lesions. Diagnosis is often difficult, however, because clinical signs may be present at different stages of life or patients may be asymptomatic, in which case the disease may be identified only by thorough investigations.

Pathologically tuberous sclerosis is characterized by lesions in many organs, but especially the skin (ungual fibromas, Pringle's type of sebaceous adenomas) and the brain: isolated tumours with a 'tuberous' appearance, and widening of the gyri, often affecting the periventricles, and with sizes varying from microscopic to that of a cherry (cardiac tumours). They are described as rhabdomyomata and considered by some authors to be benign glycogenic dystrophies (Reitano *et al.* 1985), but they can have serious haemodynamic effects because of their position. Rhabdomyoma is the most frequently-occurring cardiac tumour in newborn or young infants (Arciniegas *et al.* 1980) and in 50%

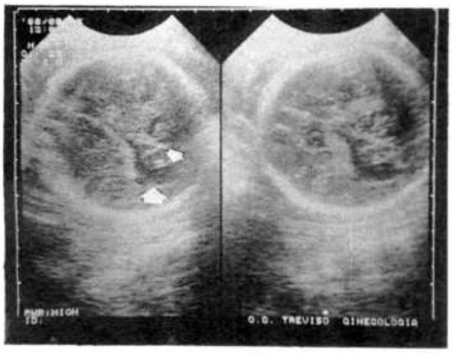

Fig. 3. Transverse section of the fetal head: left ventricle dilated on posterior horn (arrows).

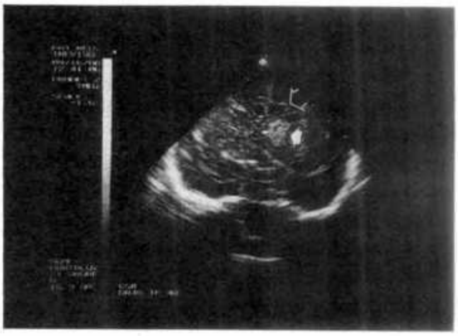

Fig. 4. Coronal section of neonatal head: dilation of left ventricle (open arrow), left subependyma tumour (solid arrow).

it is associated with tuberous sclerosis (Hausdorf *et al*. 1983). The condition is usually multiple and can involve the myocardium, endocardium, pericardium, papillary muscles, cardiac valves and the areas of pulmonary or aortic flow.

Because the parents are often asymptomatic and the main clinical signs of the disease are difficult to identify in the prenatal period, the chances of a prenatal diagnosis is limited. Cardiac symptoms (Bass *et al*. 1985, Gibbs 1985) are among the earliest signs of fetal tuberous sclerosis (arrhythmia, hydrops, rhabdomyomata), in newborn infants cardiac murmurs, cyanosis, arrhythmia and signs of cardiac failure may occur. The first prenatal diagnosis of tuberous sclerosis was made by Crawford *et al*. (1983) following the identification of a cardiac rhabdomyoma in a fetus with a positive family history of tuberous sclerosis. Since then numerous indications of prenatal and/or neonatal echographic identification of rhabdomyoma have been described, but only in 10 other cases (Plais *et al*. 1985, Muller *et al*. 1986, Journel *et al*. 1986, Plattl *et al*. 1987, Gresser *et al*. 1987, Sadoun *et al*. 1988, Monnier *et al*. 1988, Chitayat *et al*. 1988) has it been possible to establish a connection between echocardiographic findings and tuberous sclerosis. This is due either to the appearance in the postnatal period of other clinical signs typical of this disease and/or positive family history. Muller *et al*. 1986, reported the contemporary identification of a cerebral and a cardiac tumour at 25 weeks of gestation.

During the prenatal period, in the absence of a familial history, detection of a cardiac rhabdomyoma is often accidental; however, ascites, a dysrhythmia or, as in our patient, a positive family history for cardiopathy, should make the physician consider the possibility of this disease (Bass *et al*. 1985, Gibbs *et al*. 1985, De Vore *et al*. 1982).

Histological diagnosis is possible only by postmortem examination; diagnosis can be presumptive, however, based on the typical position, the multiplicity and the characteristic echo-dense aspect. Fibroma of the interventricular septum is extremely rare and may not show up on echography.

Myxoma appears as a single tumour, almost always situated in the left atrium and the interratrial septum. A myxoma syndrome has also been described (Vidaillet 1988). Other tumours are even rarer.

Even though it is non-malignant, rhabdomyoma has a high mortality (95% at 5 years), due to the haemodynamic changes and arrhythmias it creates (Fenoglio et al. 1984). These authors consider that cardiac rhabdomyoma grows only in the prenatal period and then seems to get smaller because of the increase in size of the cardiac cavities.

Chitayat *et al*. (1988) suggest the presence of an intrauterine factor of maternal or placental origin, which influences tumour growth. They also suggest early delivery whenever the cardiac tumour compromises cardiac function.

Genetic counselling after antenatal identification of cardiac rhabdomyoma must depend on the situation. If tuberous sclerosis has been identified in a parent or close relative it is most likely that the fetus is also affected by tuberous sclerosis. This is also likely if a single cardiac tumour has been clearly identified by two-dimensional echography. Even if the family medical history is negative for tuberous sclerosis and careful investigations of the parents are negative, the possibility of tuberous sclerosis cannot be excluded, since 50–80% of tuberous sclerosis are due to new mutations.

Furthermore, 50% of rhabdomyomas in newborn infants are associated with tuberous sclerosis.

At present, ultrasound detection of a cardiac or cerebral tumour is the only method for the diagnosis of tuberous sclerosis antenatally (Chitayat *et al*. 1988). But the gene for this condition has been localized on chromosome 9 (9 q34) (Smith & Simpson 1988) and it is therefore hoped that in the near future it can be specifically identified in high-risk pregnancies.

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BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting on 19 January 1990 at Guy's Hospital, London

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OD 14–an answer for hormone replacement therapy by J. Rymer, M. Chapman and I. Fogelman.* Departments of Gynaecology and *Nuclear Medicine, Guy's Hospital, London SE1 9RT.

Org OD 14 (C7α, 17α)-17-hydroxy-7-methyl-19 nonpregn-5(10)-en-20) is a synthetic compound with weak progestogenic, oestrogenic and anabolic activity and is administered orally in a daily dose of 2·5 mg. The current study involved 50 women taking OD 14 and 50 women receiving no medication. All women had had a natural menopause and both groups were matched for age and time since the last menstrual period. Areas of study included effect of symptoms, vaginal cytology, bone densitometry, serum lipids, serum GLA proteins, hormone levels and endometrial stimulation. Preliminary findings at 6 months demonstrated improvement in menopausal symptoms in 90% of women and a significant increase in karyopyknotic index and maturation index using vaginal cytology. Both total serum cholesterol and total serum triglyceride levels were significantly reduced ($P<0{\cdot}01$). Bone densitometry increased in the group of women taking OD 14, for the total spine ($P<0{\cdot}02$) and for the neck of the femur ($P<0{\cdot}04$). To date six women have had at least one episode of vaginal bleeding. Dilatation and curettage in these patients revealed no curettings and none has bled since. OD 14 appears to be an acceptable form of hormone replacement therapy and to be well tolerated by patients. Its oestrogenic effects are demonstrated by vaginal cytology, relief of menopausal symptoms and reversal of bone loss. In 180 'months use' there were six episodes of bleeding but no evidence of endometrial stimulation.

Histochemical study with an oestrogen receptor related protein in endometrial carcinoma and its correlation with biochemical oestrogen receptor status by D. Sumner, J. Kaern, K. S. Raju, V. Abeler, R. J. B. King, C. Trope. Department of Gynaecology, St. Thomas' Hospital, London and Department of Gynaecology and Pathology, The Norweigan Radium Hospital, Oslo, Norway.

The study was designed to assess the quantitative relation between cytosol oestrogen receptor (REC) and an oestrogen receptor related protein (D5) (assessed by a histochemical method) in endometrial carcinoma. Endometrial adenocarcinoma tumour tissue was collected at the time of a diagnostic curettage and/or at the time of a definitive surgical treatment. Forty seven samples were collected both for biochemical assay of REC and for histochemical study by indirect immunoperoxidase method by using D5 monoclonal antibody raised against partially purified human myometrial oestrogen receptor. Staining intensity was estimated on a 0–3 scale. REC is expressed as pmol/g of protein (>10 pmol/g REC was taken as a receptor positive tumour). Of the 47 patients 42 had REC positive tumours and five had REC negative tumours on biochemical analysis. There was positive correlation in 93% (39 patients) between histochemical staining and REC. Five patients with negative REC had positive histochemical staining and three with positive REC had negative staining with D5. There is 93% positive correlation between REC and histochemical staining with D5. This method should provide a simple alternative to a biochemical assay for REC in routine clinical practice.

Direct measurement of intrauterine fetal pressures by P. Johnson,* D. Maxwell,* L. Allan,† J. Bostock,‡ M. Tynan.‡ Departments of Obstetrics,* Perinatal† and Paediatric‡ Cardiology, Guy's Hospital, London.

The assessment of a congenital heart disease in the neonatal period is based on clinical information, non-invasive and invasive studies. At present, the only source of diagnostic information in fetal work is Doppler echocardiography. Accurate information can thus be obtained concerning anatomical normality and anomalies, but limited functional information. Intracardiac pressure means measurements provide such information. In order to correctly interpret abnormal waveforms, a reference range of normal pressures must be available. It is possible to sample fetal blood from the umbilical cord under ultrasound guidance and umbilical vascular pressures can be measured simultaneously. Alternative sites include the fetal heart. We have been recording intracardiac, intra-amniotic and intra-umbilical vascular pressures using a fluid filled system, in normal and abnormal fetuses at diagnostic blood sampling and midtrimester termination of pregnancy. Umbilical vein pressures were between 1 and 6 mmHg, with a marked elevation in three fetuses with hydrops fetalis. Cardiac pressures showed a tendency for systolic and pulse pressures to increase with gestation. In 12 fetuses left and right ventricular pressures appeared to be equal with a range of 20/4 to 80/10 mmHg from 17 to 33 weeks. Pressure waveforms show a similarity to neonatal data. In congenital heart disease, we can identify abnormal wave forms.

The stress axis in mother and fetus by C. Wolfe, P. Carabelli, A. Petruckevitch and E. Linton.* Division of Public Health Medicine, UMDS, St. Thomas' Hospital,* Department of Physiology and Biochemistry, Reading University.

Maternal and fetal umbilical blood samples, taken antenatally between 18–36 weeks in 24 subjects, were assayed for the stress hormone, corticotrophin-releasing factor (CRF), ACTH and cortisol. In the fetus blood gases were also estimated. The aim of the study is to establish the changes that occur in the circulatory levels of these hormones antenatally and the relation between maternal and fetal levels, especially in relation to labour. There was a significant rise in maternal plasma CRF, ACTH and cortisol with gestational age ($P<0{\cdot}05$) but there was no significant relation beween them. There was a significant negative correlation of fetal CRF with gestational age ($P<0{\cdot}05$) and fetal ACTH and cortisol did not alter significantly. Again there was no relation between the hormones and no correlation between maternal and fetal levels. In the fetus there is a significant downward trend in Po_2, pH and glucose with gestational age and an increase in Pco_2, with no significant trend in lacate confirming previous findings. There was no significant correlation between any of these variables and maternal or fetal stress axis hormones. Although the number of subjects is small these data may indicate possible changes in the stress axis in the fetus which require further investigation with respect to hypoxia and labour.

An evaluation of pelvic ultrasound as a screening test for women with postmenopausal bleeding by A. Rodin, K. El Farra, J. Dixon, I. Page, M. G. Chapman. Guy's Hospital, St. Thomas's Street, London SE1.

Postmenopausal bleeding (PMB) is a common presenting complaint in the gynaecology clinic and it may be the first presentation of pelvic malignancy. It is standard practice for all these women to have a dilatation and curettage (D&C) although only 15% will have significant pelvic pathology and many are elderly with co-existent medical conditions making them poor anaesthetic risks. Vaginal ultrasonography has been used to assess endometrial thickness in women with infertility and we have applied this technique to assess 70 women presenting with PMB. Blood was taken for CA 125 assay and all of these women subsequently attended for formal D&C. Ultrasound findings were abnormal in 30 women (endometrial thickness >5 mm in 27; adnexal mass in two and both abnormalities in one). Fourteen women had histological abnormalities of the endometrium and 12 of these were detected by ultrasonography including four with adenocarcinoma of the endometrium. Ultrasonography has a sensitivity of 85% and a specificity of 71% for detecting endometrial abnormalities in women with PMB. It has the advantage of allowing ovarian screening to be performed. The additional estimation of CA 125 did not improve the specificity of this screening procedure.

Non-specific renal enlargement—an antenatal marker for trisomy 13 by K. Neales, A. Saunders, C. Berry, M. Sellar, N. Fagg and D. Maxwell. Fetal Medicine Unit, Guy's Hospital, London.

Ultrasound indicators of genetic diseases are increasingly being sought as resolution and the interpretation of subtle signs improves. We report three fetuses in which the ultrasound finding of mildly enlarged echogenic kidneys was associated with trisomy 13. Renal architecture was normal although corticomedullary differentiation was not evident. Only one fetus had other abnormalities detectable by ultrasound. The next two fetuses were karyotyped antenatally following the outcome of the first fetus and both pregnancies were terminated in the second trimester. At post-mortem the kidneys were symmetrically enlarged to twice the normal weight but there were no macroscopically detectable lesions. Histologically, the renal cortices and collecting systems were normal but the medullary tissues showed some primitive mesenchymal invasion consistent with early dysplastic change. Trisomy 13 or Patau's syndrome occurs in 1 of 8000 livebirths. Various renal tract abnormalities have been reported including hydronephrosis, prune belly syndrome and renal cortical cysts. The commonest abnormalities detectable by ultrasound in trisomy 13 are midline cranial and facial defects. We conclude that non-specific renal anomalies, such as mild enlargement and increased echogenicity may be an indication for an urgent karyotype and that the spectrum of disease in these fetuses is different from that seen at term. In our experience trisomy 13 is particularly associated with these changes which may prove to be reliable antenatal markers.

Most gynaecological emergencies can be managed laparoscopically by A Magos, R. Baumann, Sir A. Turnbull. Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Maternity Department, Headington, Oxford OX3 9DU.

In 1988, 104 operative gynaecological laparoscopies were carried out in Oxford, and the 67 emergency procedures have been reviewed in detail. Indications included women who were haemodynamically stable with acute lower abdominal pain, pelvic tenderness and either a positive sensitive urinary pregnancy test or a pelvic mass of <10 cm diameter on clinical examination or ultrasound. The mean age of the study group was 27·4 years, 14 having undergone one or more laparotomies previously. A three-puncture approach was used in most patients. Operative findings included ectopic pregnancy (38), of which 79% were leaking or ruptured, ovarian cystic accident (18), adhesions (3), endometriosis (2), fibroids (2), and miscellaneous others (4). Laparoscopic procedures included ovarian or parovarian cystectomy, salpingectomy and salpingotomy, extraction of ectopic pregnancy, adhesiolysis, endocoagulation, and myomectomy. Intra-abdominal suturing was used in 31 patients. Four (6%) women required laparotomy. For the successful cases the mean operative time (defined as the intubation-extubation interval) was 60 min, the post-operative hospital stay 1·8 days, and the time taken to return to normal activities and work 2·0 and 2·4 weeks respectively. We conclude that most gynaecological emergencies traditionally managed by laparotomy can be treated laparoscopically to the benefit of both patients and health service.

The diabetic intrauterine milieu induces long term effects of insulin resistance by F. A. van Assche, K. Holemans and L. Aerts. Departments of Obstetrics and Gynaecology, University Hospital, Leuven, Belgium.

We have shown previously in the rat that the fetal development in an intrauterine diabetic milieu results in a decreased insulin secretion and an increased insulin resistance in later life. These data have been confirmed in the human (Pima Indians). The postulated insulin resistance in the adult offspring of severely diabetic rats (SDF) was further investigated using the hyperinsulinaemic clamp technique combined with an isotope-dilution method. The effect of three concentrations of insulin on glucose production and utilization was studied in SDF rats and in well-matched controls. Glucose kinetics were determined by (3-$_3$H)-glucose. In the *basal* state, no significant differences between the two groups were found. Glucose *infusion* rates were lower in SDF-rats than in C-rats. Glucose *production* in C-rats was totally suppressed at plasma insulin concentrations higher than 1200 μU/ml. In SDF-rats glucose production could not be totally suppressed from a basal rate of 1·97 ± 0·10 mg/min and 1·95 ± 0·09 mg/min to a minimum of 0·16 ± 0·04 mg/min and 0·84 ± 0·05 mg/min at plasma insulin concentrations of 3900 ± 320 μU/ml and 5700 ± 760 μU/ml in respectively C-rats and SDF-rats ($P<0·001$). Maximal glucose *utilization* occurred at insulin concentrations of 1000 μU/ml in C-rats and 250 μU/ml in SDF rats. C-rats and SDF-rats were compared with the *t*-test or Wilcoxon analysis as appropriate. Differences were considered significant if $P<0{\cdot}05$. These data provide evidence for the existence of insulin resistance in offspring of severely diabetic rats (SDF) and is characterized by a decreased sensitivity and responsiveness of the liver to insulin, and a decrement of insulin sensitivity in the peripheral tissues.

A double blind cross over-trial of mebeverine against placebo and against mefanamic acid in the treatment of primary dysmenorrhoea by A. F. Langrick,* H. Livesey,† and A. M. Whitehead.† *University of Birmingham Health Center and †Duphar Laboratories, Southampton.

A double blind, three-way cross-over trial of mebeverine hydrochloride against placebo and against mefenamic acid in the treatment of dysmenorrhoea in general practice was carried out over three menstrual cycles. Drug dosage was two capsules thrice daily (2 × 135 mg mebeverine; 2 × 250 mg mefenamic acid; 2 capsules placebo). Paracetamol was permitted as a rescue analgesic. Data were analysed from 49 patients. Relative efficacies of the three treatments were compared by analyses of variance. All treatments (including placebo) demonstrated significant superiority over no treatment in relieving pain severity and disruption to normal activities. Both mebeverine and mefenamic acid were superior to placebo in reducing the severity of pain ($P<0{\cdot}01$ and $P<0{\cdot}02$ respectively). Only mefenamic acid demonstrated significant superiority over placebo in reducing the level of disruption to normal activities ($P<0{\cdot}05$). A trend was apparent towards mebeverine reducing the severity of abdominal bloating and nausea. Treatment with mefenamic acid significantly reduced the amount of paracetamol consumed ($P<0{\cdot}01$). There were seven reports of treatment emergent signs and symptoms; five during treatment with mefenamic acid, and one each during treatment with mebeverine and placebo. Thus mebeverine can be considered an alternative to mefenamic acid in the treatment of dysmenorrhoea.

Systematic evaluation of clinical criteria, ultrasound and CA125 to achieve accurate pre-operative diagnosis of ovarian cancer by I. J. Jacobs, J. Fairbanks, C. Frost, J. G. Grudzinskas and D. H. Oram. The London Hospital, Whitechapel, London E1 1BB.

This study was undertaken to determine the value of clinical criteria, ultrasound and serum CA 125 in the differential diagnosis of benign and malignant pelvic masses. The study population consisted of 143 consecutive patients undergoing elective surgical investigation of an adnexal mass. Significant differences ($P<0{\cdot}01$) were observed in age, menopausal status, clinical impression score, ultrasound score and serum CA 125 between patients with benign ($n=101$) and malignant disease ($n=42$). The most useful single diagnostic criteria were CA 125 (sensitivity 81·0%, specificity 75·2%), and ultrasound (sensitivity 70·7%, specificity 82·7%). Logistic regression analysis revealed that the highest diagnostic accuracy could be achieved by the combined consideration of menopausal status, ultrasound and CA 125 (sensitivity 85·4%, specificity 98·0%). A clinician using this formula to select patients for specialist referral, would expect to correctly classify >90% of patients with benign and malignant disease. This approach provides a rational basis for pre-operative referral of patients in the high risk group for specialist care.

Analysis and prospective follow-up of 260 women referred with unexplained recurrent miscarriage by G. H. Ramsden, P. M. Johnson and R. G. Farquharson. Department of Immunology, Royal Liverpool Hospital and the Women's Hospital, Liverpool.

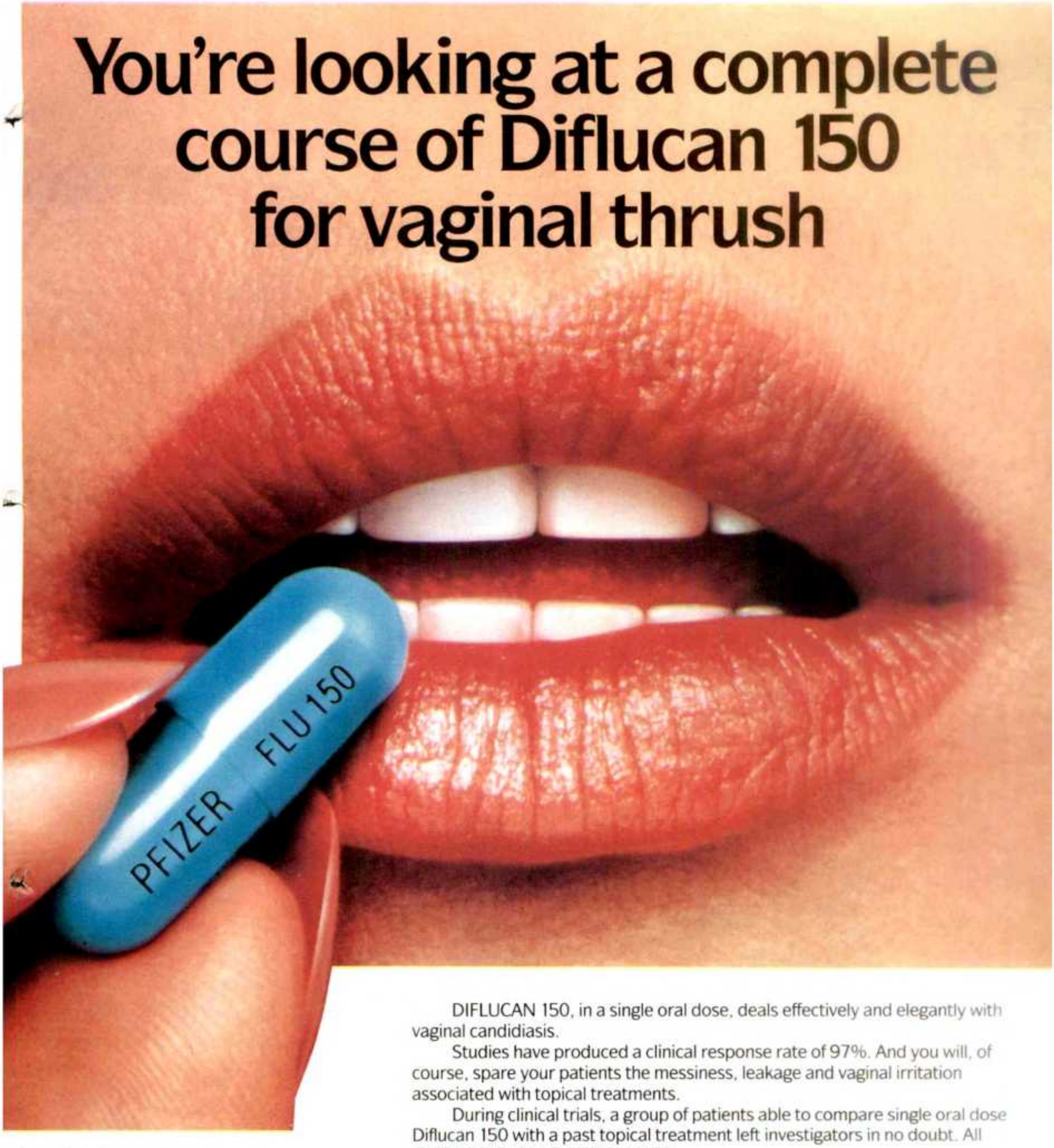
The study included 260 women referred with unexpected recurrent miscarriage (RM) who have been assessed and followed up at either the University Department of Immunology, Royal Liverpool Hospital, or the Miscarriage Clinic, Women's Hospital, Liverpool. Twelve (5%) had SLE or the presence of lupus anticoagulant and a further 14 (5%) revealed various other defined aetiologies which include abnormal parental karyotype, cervical incompetence and maternal medical disorders. The other 234 (90%) remained with an unknown aetiology of which a subgroup of 172 gave laboratory results that could be compatible with a failure of maternal immunological adaptation to the developing conceptus. Eighty-one RM women received immunotherapy in an open study based on a trophoblast membrane infusion (TMI), and a further 52 women were entered into a double-blind randomized placebo-controlled trial. The overall livebirth success rate for women receiving TMI was 60% (58 pregnancies) compared with a livebirth success rate of 67% (39 pregnancies) for those women who fulfilled criteria for TMI but received placebo or pre-empted treatment by becoming pregnant. Thus, it is difficult to establish a clear aetiology in the majority of unexplained RM women, and treatment therapies have to be interpreted in the light of a significant spontaneous livebirth success rate.

Maternal low-dose aspirin spares neonatal platelets by K. A. Louden, F. Broughton-Pipkin, S. Heptinstall, J. R. A. M. Mitchell and E. M. Symonds.

Aspirin use in pregnancy has been considered unwise until recent suggestions that low doses may prevent pre-eclampsia. We have used a longitudinal, randomized, double blind, placebo-controlled design to investigate the effect of 60 mg aspirin daily on three variables of platelet function. Non-pregnant female volunteers (NFV, n=12), normal primigravidae (NP, n=18) and primigravidae who developed pregnancy-induced hypertension (PIH n=16) were studied, and umbilical cord blood samples were obtained at delivery. The NFV group were studied before and after a 10-day course of aspirin, whilst the NP and PIH groups were randomized to receive either 60 mg aspirin, or placebo, from 16 weeks and from diagnosis respectively, to be taken daily until delivery. The advantages of whole blood techniques were employed to study platelet aggregation (PA), whilst release of radio-label from pre-loaded platelets was used to measure the 'release reaction' (RR). Serum thromboxane B_2 production was measured by radio-immunoassay. Results are shown in the table, expressed as % reduction in median value after low dose aspirin. Profound inhibition of platelet function was seen in all of the adult groups, but a considerable sparing effect on the newborn was noted, which may be important if low-dose aspirin is to become a useful therapeutic option in obstetrics.

	NFV	NP	PIH	Normal Baby	PIH Baby
Arachidonic acid-induced PA	61	74	55	2*	62*
Arachidonic acid-induced RR	100	93	97	12*	17*
Serum thromboxane B_2	97	89	90	74	0*

*Indicates those changes which did not reach statistical significance (P<0·01).



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British Journal of Obstetrics and Gynaecology
December 1990, Vol. 97, pp. 1163–1164

CORRESPONDENCE

Modern treatment of menorrhagia (Commentary)

Dear Sir,

Although the commentary by Russell Macdonald [Br J Obstet Gynaecol (1990) **97**, 3-7] gave a well-rounded review of current treatment for menorrhagia, certain points relating to endometrial fibrinolysis and the use of antifibrinolytics in menorrhagia were somewhat misleading. The commentary states that no clear difference in uterine fibrinolysis has been demonstrated between women with normal menstrual blood loss (MBL) and those with demonstrable MBL of >80 ml. To the contrary, investigations of endometrial biopsy specimens taken at various points throughout the cycle demonstrate quite clearly that endometrial fibrinolytic activity increases dramatically just before menstruation (in normal and menorrhagic women) and that women with objectively measured MBL of >80 ml per period have significantly higher fibrinolytic activity at the onset of menstruation than those with blood loss of <80 ml per period (Rybo 1966).

To state that the mode of action of tranexamic acid is unclear is also unfounded. It is well established that tranexamic acid competes for the lysine binding sites of the plasminogen molecule which are essential for it binding to fibrin. This prevents activation of plasminogen by plasminogen activators at the fibrin surface (Thorsen 1975, Hoylaerts *et al* 1981). Fibrinolytic activity in menstrual blood is reduced to normal levels in women complaining of menorrhagia treated with tranexamic acid (Bonnar *et al.* 1983).

Finally, about Mr Macdonald's statement that the long-term use of tranexamic is restricted by the risk of inducing thrombosis, again I can find no evidence to substantiate this. Indeed a retrospective review of the use of tranexamic acid for menorrhagia over a 19-year period in Sweden showed the calculated incidence of thromboembolic episodes in an estimated 238 000 patient-years of treatment to be no greater than the spontaneous incidence of thrombosis in fertile women (S. Ekman and B Karlmark, Kabi Internal Report 1988).

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Author's reply

Dear Sir,

The effectiveness of tranexamic acid for the treatment of menorrhagia is not in doubt. Results are similar to other commonly used agents (Macdonald 1990). It may even be superior; other countries such as Sweden, where it is considered suitable for long-term use, have lower hysterectomy rates.

The mode of action of the drug is also clear. It is a potent antifibrinolytic agent (Astedt 1987). However, evidence of deranged fibrinolysis and therefore the rationale for its use in menorrhagia is not so clear. When menorrhagia is diagnosed subjectively, plasminogen activator and plasmin activity are significantly higher than in the menstrual blood of 'normal' controls (Dockeray *et al.* 1987). When more accurate diagnosis is made by measuring menstrual blood loss, the evidence is less convincing. Rybo (1966) found a significant increase in endometrial plasminogen activity, but only on day one of menstruation and in a selected group of patients. Rees (1985) measured a wide range of coagulation factors and fibrinolytic proteins in menstrual blood and failed to find a significant difference.

Is tranexamic acid safe for long-term use? Retrospective evidence from S. Ekman & B. Karlmark (Kabi Internal Report 1988) indicate that it is, but doubts have been expressed (Committee on Adverse Drug Reactions, Sweden 1980) and there are case reports of thrombo-embolic complications (Rydin & Lundberg 1976; Davies Howell 1977; Agnelli *et al.* 1982).

Tranexamic acid significantly reduces plasminogen and plasmin activity levels in menstrual blood of patients with menorrhagia, but it also causes a significant drop in plasminogen and plasmin activity in peripheral blood (Dockeray *et al.* 1987). Although the activity of vascular endothelial plasminogen activator is not affected (Astedt *et al.* 1978), tranexamic acid may prolong the dissolution of previously formed fibrin deposits (Astedt 1987). Patients predisposed to fibrin deposition may therefore have a theoretical risk of developing thrombo-embolic problems.

In addition, the British Pharmaceutical Industry Compendium states that the use of tranexamic should be restricted to three cycles. It is therefore difficult for clinicians to recommend more long-term use.

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London N7

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BOOK REVIEWS

Modern Antenatal Care of the Fetus, edited by Geoffrey Chamberlain. Blackwell Scientific Publications, Oxford, 1990, 436 pages, with figures and tables, £49.50

Modern Antenatal Care of the Fetus is a treasure trove of references; a source of concise up-to-date (as current as production delays allow) information assembled in a novel way which concentrates on the fetus and virtually bypasses the mother.

Inevitably the galaxy of authors contribute in different styles but as style changes with subject matter the end result is a pleasing and satisfactory cohesion. The reader may require specialist text to augment a topic but the detail provided in each chapter provides an excellent working overview of each subject. Most sections comprise a synopsis of the current state of the art under discussion together with an historical review and forecast of possible developments.

Some chapters have also placed emphasis on the basic science background where required. The authors are obviously enthusiasts but it is good to see that on the whole most retain a healthy scepticism and advise appropriate caution. There is repeated emphasis on the need for validation before widespread adoption of new techniques and it is to be hoped that readers will follow this wise advice.

This book will be an important addition to the bookshelf of all those working in the field of perinatal medicine and in addition membership candidates will find a wealth of information presented critically, that style of presentation is to be commended to them.

The mix of old and new is stimulating. The masterly chapter on the placenta will be read avidly by all students from the undergraduate to the retired, while the exciting concept of decision analysis, although perhaps somewhat obscure and difficult for the aged to grasp, opens new vistas, setting the art of the specialty on a firmer scientific footing. In contrast, interest in biochemical testing, regarded by many as outmoded, is renewed here in relation to potential markers of fetal wellbeing. Predictably, of the 20 chapters, nine are concerned with imaging techniques with exceptional illustrations and one could be forgiven for believing that ultrasound is set to replace all clinical skills but the authors are moderate and critical in their views and claims.

It is a well produced book that is value for money and apart from an irritating split infinitive or two, educates and stimulates the reader, encouraging critical thought.

Gillian M. Turner

Obstetrics, edited by Sir Alec Turnbull & Geoffrey Chamberlain. Churchill Livingstone, Edinburgh, 1989, 1200 pages, with figures and tables, £95.00

As the preface of this book says—although many books have been written about specialized aspects of obstetrics there is a dearth of major books covering the whole modern field. This book fills that void and provides a very comprehensive review of all aspects of modern obstetrics. The authors have accumulated a galaxy of talent amounting to 89 different authors—all experts in their individual fields and are the names of all those who have made important contributions to the speciality. There are 15 sections starting with basic sciences, through modern antenatal care, abnormal pregnancy, normal and abnormal labour and the puerperium and newborn. There are also sections on assisted pregnancy, vital statistics and contraception and the last section details the medico-legal aspects of obstetric problems today.

In addition to the chapters by obstetricians on a wide spectrum of the speciality the authors have included chapters by non-obstetricians who have been critical of modern obstetrics. Ann Oakley, for example, sets out clearly her criticism of the way modern labour is conducted and gives the views of the consumer movement in maternity care. There is also an excellent chapter by Gillian Forrest on parental appreciation of perinatal death which is much to the fore these days.

Every aspect of obstetrics is covered and it will be a 'bible' for all those reading for higher examinations in the speciality. The chapters are all well referenced and as up-to-date as possible in a book with so many contributors. This is a tribute to the editors.

The only drawback of a comprehensive textbook like this is that new innovations in obstetric care are constantly being introduced so that certain chapters rapidly become out of date. This, however, does not detract from an excellent book which all obstetricians should have for reference. This is of particular importance nowadays since many clinicians do not see some of the rarer complications and will find good advice in this book on almost everything that can occur in obstetrics.

Malcolm MacNaughton

Basic Adolescent Gynecology: An Office Guide, edited by Victor C. Strasburger. Urban & Schwarzenberg, Baltimore, Munich, 1990, 243 pages, with figures and tables, £39.25

The title of this book is misleading, as it implies that it is a book written for gynaecologists and, whilst there is information for gynaecologists, this book is written by paediatricians primarily for paediatricians. It covers all the medical aspects of gynaecological problems in adolescents but the emphasis is entirely upon the medical treatment and is really very limited for gynaecologists. The chapter on adolescent sexuality is enlightening and probably the best chapter in the book. The formulations and prescribing are entirely American and therefore inappropriate for British gynaecologists. One section provides a colour guide to gynaecological problems but is rather poor and does not cover adequately many of the gynaecological problems that we see and the quality of the clinical photographs leaves a considerable amount to be desired. I found this book disappointing and I doubt whether it will find a place on the library shelves in the United Kingdom.

D. Keith Edmonds

Intrauterine Growth Retardation. Nestle Nutrition Workshop, Series Volume 18, edited by Jacques Senterre. Raven Press, New York, 1989, 332 pages, with figures and tables, $57.00

A hospital without running water or electricity cannot provide sophisticated care during pregnancy. Ultrasound examination and electronic monitoring of the fetus would not be part of antenatal surveillance there. The staff could, however, improve perinatal and maternal mortality and morbidity by working in co-operation with their community medical colleagues and with local politicians. As this book demonstrates intrauterine growth retardation is a significant factor both in perinatal death and in long-term handicap around the world and a constant refrain is its relation to social deprivation and to smoking. There are many other relevant factors such as infection but most are related to poor social circumstances. The first steps in remedying these must be both medical and political. It is the medical approach which this volume reviews in stimulating fashion. Stimulating not from any polemical attempt but because it is the record of a conference of experts who were not reluctant to question assumptions or data. The reader will certainly learn from it although, perhaps, will not agree with all that was presented or discussed.

Fundamental physio-pathology introduces the subject at the high level of inquiry and knowledge that is sustained throughout. Reference ranges for birthweight have a chapter to themselves and recur in many of the discussions. Chapters on the assessment of fetal growth during pregnancy are followed by discussion of its significance to future development. Data are given from Africa, from India and Bangladesh, from South America and from Italy.

The relevance of maternal nutrition to fetal growth and to later development is explored in detail. To read the chapters and the discussion which follows them will produce understanding of the problem world wide. Politicians are unlikely to read the book but they might seek advice from those who have. Advice needs thought. Effective advice requires thought nourished by data. This conference may have helped some advisers by producing the data and by providing the opportunity to digest this with an appetite stimulated by the many opinions which fill the discussion. Those who want to learn more about intrauterine growth retardataion will also enjoy reading this mixture of clearly presented relevant data, flavoured with informative comment by the other participants. A worthwhile workshop.

Iain McFadyen

Human Genetic Information, Law and Ethics (Ciba Foundation Symposium 149), edited by D. Chadwick, G. Bock & J. Whelan. John Wiley and Sons, Chichester, 1990, 211 pages, with figures and tables, £39.95

The Ciba Foundation is renowned for organizing Symposia which gather together a select group of experts to discuss topics of contemporary medico-scientific importance. This book, the product of the 280th Symposium, is a fine example of the high quality which such meetings achieve. The subject is topical—worldwide, work is beginning on, and a huge quantity of public money is being committed to, mapping and sequencing the entire human genome. Society generally has a certain fear and distrust of such work. This book airs the scientific, legal, ethical, social and economic issues which arise. The beauty of Ciba meetings is that the discussions are included as well as the formal papers. The book is informative and readable, although the complexities are not shirked. It starts by considering the present position and what achievements are expected in the next decade. It exemplifies how knowledge of the genome helps the understanding of genetic defects, its application to increasing our prenatal diagnostic repertoire, and its unique ability to reveal the distinct individuality of all humans. Particularly enlightening is the contribution it is on the verge of making to psychiatric illness. Somatic gene therapy is considered imminent and a most useful tool, but germ line therapy is not welcomed because, in animals, it has had unexpected side effects and risks. Over half the book is devoted to considering how the research should be applied to human welfare. Questions are asked about the philosophical, religious, ethical, legal and commercial implications of this new knowledge. How will it influence our perceptions of ourselves as unique individuals and our concepts of human nature? Who has the right to know, and hold, such intimate information about ourselves? How do the major world religions receive the work? Who will be justified in making money out of DNA? The book is highly recommended both for its science and for its coverage of issues of social concern.

Mary J. Seller

Fetal and Neonatal Body Fluids: The Scientific Basis for Clinical Practice (Reproductive and Perinatal Medicine (11)), edited by Robert A. Brace, Michael G. Ross & Jean E. Robillard. Perinatology Press, Ithaca, New York, 1989, 372 pages, with figures and tables, $105

This is the latest in an excellent and much needed series, published by Perinatology Press, which integrates recent findings in the basic sciences with clinical topics in perinatal medicine. Fluid and electrolyte balance in the fetus and in the neonate differ greatly from that of the adult. There have been a number of advances in the past few years in our understanding of fluid balance during pregnancy and its regulatory mechanisms, making this volume a timely review. The book is divided into five parts and 15 chapters, with authors mainly, but not exclusively, from North America and Australia. They represent a variety of clinial and scientific disciplines.

The first part deals with the fetus itself, its blood and other extracellular fluids, swallowing, lung and renal function; it includes a useful review of a complex pathological subject, hydrops fetalis. The second part considers amniotic fluid, its composition and regulation, and the aetiology and significance of too little and too much. The uncertain nature of the relationship between prolonged oligohydramnios and pulmonary hypoplasia is explored, as is (in another chapter) a novel hypothesis to explain polyhydramnios. A brief section on placental transfer is followed by others on maternal fluid balance during pregnancy and on the passage from fetal to neonatal existence (including that of the preterm baby).

The editors aimed at a comprehensive review of fetal and neonatal fluid and electrolyte balance, suitable for clinicians and scientists, including those seeking an introduction to the subject. They have succeeded well. The contributions are well written and scholarly throughout. The material is up to date (atrial natriuretic peptide features prominently). The book is highly recommended. I look forward to more of this series.

J. P. Neilson

Quadruplets and Higher Multiple Births (Clinics in Developmental Medicine No 107) by Marie M. Clay. MacKeith Press, London, 1990, 186 pages, with figures and tables, £20.00

The author is an educationist, who is mainly concerned with the rearing and psychological development of quadruplets and the children from other higher multiple pregnancies. The infrequency of and the failure to document and study these children has resulted in little factual information being available. Few conclusions therefore have been reached that could guide educationists and parents in rearing these children. Half of the book is composed of an appendix with brief histories and some photographs of 142 sets of quadruplets obtained from papers published over the 150 years until 1984.

For the obstetrician and gynaecologist this book serves as a reminder, if one is needed, of the importance of avoiding the artificial production of higher multiple births with their attendant problems.

Ian MacGillivray

Books received some of which will be reviewed at a later date.

Prenatal Diagnosis and Prognosis edited by Richard Lilford. Butterworths, London, 1990, 245 pages with figures and tables, £39.50

Reproductive Medicine and the Law edited by A. A. Templeton and D. Cusine. Churchill Livingstone, Edinburgh, 1990, 192 pages, £29.50

Handbook of Ultrasound and Gynecology Vols. I and II edited by Asim Kurjak. CRC Press, Boca Raton, 1990. Volume I, 1—360 pages, Volume II 1—317 pages, both books are fully illustrated, £120

Endoscopic Laser Surgery (Clinical Practice of Gynecology Vol. 2 No 1 1990) edited by Michael S. Baggish. Elsevier, New York, Amsterdam, London, 1990, 233 pages fully illustrated, $35.00, Dfl 82.50.

Common Problems in Infertility and Impotence edited by Jacob Rajfer. Year Book Medical Publishers, Inc. Chicago, London, Boca Raton, 390 pages fully illustrated, £51.00.

How to Avoid Medico-Legal Problems in Obstetrics and Gynaecology edited by Geoffrey Chamberlain & Christopher Orr. Produced by Members of the Joint Medico-Legal Committee of the Royal College of Obstetricians and Gynaecologists and Medical Defence Organizations. The Chameleon Press Ltd, London, 1990 and available from the Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG, 81 pages £4 plus packing and postage (40 pence UK)

Clinical IVF Forum. Current Views in Assisted Reproduction edited by Phillip L. Matson and Brian A. Lieberman. Manchester University Press, Manchester and New York, 1990, 150 pages illustrated £12.95

The Johns Hopkins Handbook of In Vitro Fertilization and Assisted Reproductive Technologies edited by Marian D. Damewood, Little Brown and Company, Boston, Toronto, London, 1990, 176 pages, 40 illustrations, £19.95

Green's Gynecology. Fourth edition edited by Daniel L. Clarke-Pearson, M. Yusoff Dawood and Charles B. Hammond. Little, Brown and Company, Boston, Toronto, London, 1990, 672 pages, 135 illustrations, £29.95

A Colour Atlas of Life Before Birth. Normal Fetal Development by Marjorie A. England. Wolfe Medical Publications Ltd, London 1990, 216 pages fully illustrated with colour plates. Hardback £37, paperback £14.95

African Birth. Childbirth in Cultural Transition by Beverley Chalmers, Berev Publications, South Africa, 1990, 140 pages illustrated, available from Berev Publications CC, P.O. Box 107, River Club 2149, South Africa, $17.50 (plus $2.50 for postage and handling)

Proceedings and Symposiums

Female Urinary Incontinence (Proceedings of an Educational Course held at the Royal College of Obstetricians and Gynaecologists, June 1989) edited by G. J. Jarvis. Published by the Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG, 89 pages £6.00

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